FILE DESCRIPTION

PHILADELPHIA FILE

SUBJECT HARRY GOLD

FILE NO. 65-4307

VOLUME NO. 1-B-14

SERIALS —

NOTICE

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Inventory Worksheet
FD-503 (2-18-77)

VOLUME Bulky

PHILADELPHIA FILES

INVENTORIED BY CKK

REVIEWED BY DP

File No: 65-4307-1-B-14 Re: Harry Gold

Date: 5-30-78 (month/year)

Serial	Date	Description (Type of communication, to, from)	No. of Pages Actual	No. of Pages Released	Exemptions used or, to whom referred (Identify statute if (b)(3) cited)
1-B 14	6-6-50	FD 141 Bulky Exhibit Items 1-5	1	1	
Enclosure #1	6-6-50	Envelope	2	2	
—	6-6-50	Mothproofing notes	4	4	some parts are illegible
—	6-6-50	Butylene Glycol notes	1	1	
—	6-6-50	Belle Meade letterheads	2	2	
Enclosure #2	6-6-50	Envelope	1	1	
-	6-6-50	Chemical analysis	21	21	
- Enclosure #3	6-6-50	Folder	1	1	
-	6-6-50	Photocopies & cover sheet	8	8	
-	6-6-50	Notes on Nicotinic Acid	18	18	
Enclosure #4	6-6-50	Envelope	1	1	
-	6-6-50	Notes on Pantothenic acid	39	39	

FBI/DOJ

Inventory Worksheet
FD-503 (2-18-77)

VOLUME Bulky PHILADELPHIA FILES

INVENTORIED BY ckk

REVIEWED BY

File No: 65-4307-1-B14 Re: Harry Gold

Date: 3/78 (month/year)

Serial	Date	Description (Type of communication, to, from)	No. of Pages Actual	No. of Pages Released	Exemptions used or, to whom referred (Identify statute if (b)(3) cited)
—	6-6-50	Photocopies	41	41	
—	7-15-46	Ltr. Aircraft Corp to a. Brotman and Assoc	1	1	
Enclosure #5	6-6-50	Folder & Envelope	2	1	
—	6-6-50	Notes on Pyridoxin	52	52	
—	6-6-50	Photocopies	31	31	

FBI/DO

FD-11
(7-1-48)

BULKY EXHIBIT

Date received June 6, 1950

HARRY GOLD

ESPIONAGE - R

(Title of case)

Submitted by Special Agent ROBERT E. MASTERS

Source from which obtained SEARCH OF SUBJECT'S RESIDENCE

Address 6823 Kindred St., Phila

Purpose for which acquired Aid in investigation

Location of bulky exhibit Bulky Exhibit Room

Estimated date of disposition 12-1-50

Ultimate disposition to be made of exhibit to be determined

List of contents:

Envelope, brown manila marked Re-org 3-29-46 from Harry Gold's bedroom
Envelope, brown manila, marked Re-org 3-29-46
Manila folder marked Photocopies Nicotinic Acid
Manila folder marked Pantothenic Acid
Manila folder marked Nicotinic Acid

Return 5/3/51 RS

Return 11/14/51 RS

Returned 11/16/51 RS

Returned 6/27/52

65-4302-4B-14

FBI - PHILADELPHIA
JUN 22 1950

#1

June 6, 1950

Joseph Gold
(Name of Contributor)

6823 Kindred St, Philadelphia, Pa.
(Address of Contributor)

By Robert G. Masters
(Name of Person Mailing)

To Be Returned: Yes / No

Description: 1 p. Envelope, brown manila, marked Reg. 4/24/50 from Harry Gold - Chelsea

File No. 65-F307-1-B-14

Re-orig. 3-29-46

1. Belle made attendance

2. Beautician daily [illegible]

3. Doris [illegible]

[illegible]

I

Mothproofing — In recent years the mothproofing of woolen and worsteds has gained in importance because of the discovery of effective chemical compounds, and more simple applications. There is a definite place for satisfactory mothproofing for all wool goods which are stored during certain periods of the year, such as wearing apparel and blankets — This need is also desired in upholstery, carpeting and other bulky materials, which, once infested can only be fumigated.

While there are many compounds recommended for this purpose there are only a few which are really effective over a long period of time. For treatment by the woolen manufacturer the following types of compounds have found extensive application — Rotenone — Pelaris silico-fluoride — Thanhouse, Albright assaying-51 — Merck — only Chem. Abst. cited

directions in the fabric which is infested - it has also been reported as destructive to furs.

Cloth moth { Tinea pellionella L.
Tineola biselliella (Hummel)

feed on wool - fur - hair - feather and all fabrics made from them & the related dried matter such as dead insect, etc.

life cycle

egg - larva, the pupa and the moth.

The moth or miller which is the adult seldom lives as long as one month - usually dies between the 7th and 14th day after the emergence from the pupa - they do not take no nourishment. The female moths start laying eggs before they are fully 1 day old and usually lay eggs each day of their life - when she stops laying eggs it means she will die in a day or so. She lays about 100 to 150 eggs and ½ of the number in the first few days of her life.

6/6/12

Tests made by Sprangle and Clabaugh disclose that "silico-fluorides" are effective as initially applied to fabrics, are not removed by dry cleaning solvents and are not deteriorated by light - however they are removed by washing

Chinchona alkaloids and Rotenone are effective as initially applied to the fabrics, are not removed by washing but are removed by dry cleaning solvents and are deteriorated by exposure to light

Eulan CN and Eulan NK are produced by General Dyestuff Corp and can be applied to piece goods during dyeing process they are not removed by washing

" " " " dry cleaning

" " " " deteriorated by exposure to light

they are effective as initially applied to fabrics

Carpet Beetles — (called "Buffalo" moths)
(they get in wall spaces and hide during cleaning agitation)

1 - Common Carpet Beetle - (Anthrenus scrophulariae L.)
2 - Furniture Carpet Beetle - (A. vorax = Waterh.)
3 - the Varied Carpet Beetle (A. verbasci L.)
4 - Black Carpet Beetle (Attagenus piceus - Oliv.)
None more than 1/4 inch - adults are hard shelled - oval.

Only larvae or grubs of carpet beetle cause damage -

The larvae shun light and get in darkened places - particularly articles lying on floors & about the edges of carpets and under base boards)

Moths - Common species of clothes pests

There are 3 very common species -

1- Case-making cloth moth - (Tinea pellionella L.)

2- Webbing clothes moth (Tineola biselliella - Hummel)

3- Tapestry moth - (Trichophaga tapetzella L.)

1- Tinea pellionella L - wing spread ½ inch, head is grayish yellow or buff - wings are white & satiny (Called Case making because the larva for its protection, makes a portable case out of spun silk and fragments of the fabric on which it feeds) - the larva almost never leaves its case - when resting it goes in completely - when eating or moving about it merely protrudes its head - the larva spins almost invisible webs on the fabric on which it feeds. And is more likely to crawl about, aimlessly, eating small holes.

Webbing moth - (Tineola biselliella Hummel) same size as above - but color is uniformly pale buff - no spots - never over ½ inch wing spread

the webbing moth is most abundant and really injurious to clothes - in the last few years nearly all the damage reported from big flats in the North - Chicago, Boston &c have been caused by the species. The larva of the webbing clothes moth resembles that of the case making moth - but it does not make a portable case - it spins a silky tube or tunnel wherever it goes: often spins a cobwebby mass of silken threads at random - the larvae may be quite restless and often may be seen crawling over fabrics or upholstery - at full growth it spins a cocoon and in this cocoon the transformation from larva to adult moth takes place, as in the case in other species the Chrysalis works its way partly out of the cocoon as the moth is about to emerge.

Tapestry moth (Trichophaga tapetzella L.) (not common in U.S. as the above two) and considerably larger (3/4" long) and colored - prefer heavier fibres - (carpets - horse hair) the larvae construct burrows or silk tubes

head is black - and blankets, furs, felting &c woollen or silk

Stanton Lab — Phila

Conc = 300°/00

Titre = 6 1/2 cc

pH = 5.4

Sp. Gr. = 1.212/20°C

Iron = 5 ppm

Copper = 4.5 ppm

Nitrite = Trace

Diethyl glycolic acid = 18%

Glycerine = None

Diethyl glycolide = None

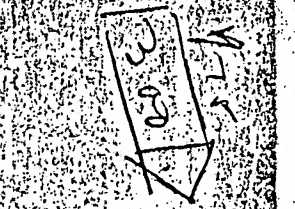
Color = Dep. Yellow

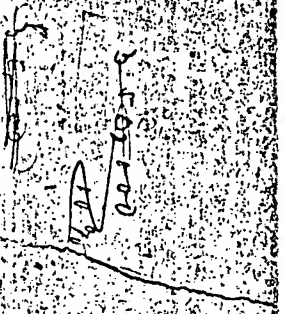
Rec'd 6/15/51

Wednesday

1876 10 Oct

Color - Pink to Brown





2,3 - Butylene Glycol

organism - Aerobacter aerogenes
(A. aerogenes No. 199)

medium for Fermentation

0.5% corn steep liquor
0.5% calcium carbonate
5% glucose

Inoculum 3-5% Patch

Reducing sugar content 12.0 gm / 100 cc
Fermentation time 42 hrs

Isolation

Fermentation medium / liter

3 gm. KH_2PO_4
3 gm. Urea
5 gm. $CaCO_3$

Look for Northern Regional Lab. article
Dec. 1945 (1 8 9 -

DISTILLERY PERMIT NO. SD12

VA. A. B. C. LICENSE NO. 852

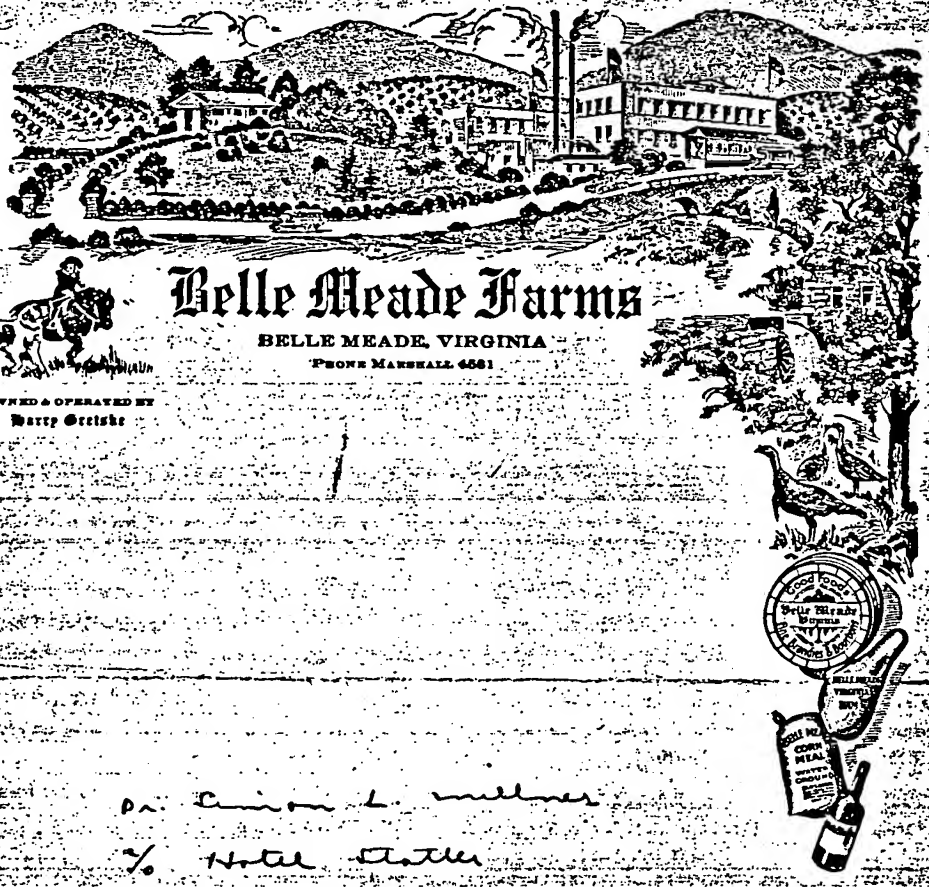
Belle Meade Distilling Corporation

DISTILLERS

BELLE MEADE, VIRGINIA

TELEPHONE: MARSHALL 6581

Qur. #2
6/6/50



Belle Meade Farms

BELLE MEADE, VIRGINIA

PHONE MARSHALL 4581

OWNED & OPERATED BY
Harry Greiske

Dr. Simon L. Miller
% Hotel Statler
Wash., D.C.

#2

Received June 6, 1950

Joseph Gold
(Name of Contributor)

6823 Kindred St. Philadelphia, Pa.
(Address of Contributor)

By Robert J. Master
(Name of Special Agent)

To Be Transmitted Via (✓)
Airtel ( )
Teletype ( )

Report of 2 Envelopes, Cover Memo, Dated 6-2-50

File No. 65-4207-1B-14

Quantitative chemical analysis

I Concentrations of materials

II Gravimetric analysis

III Volumetric analysis

IV Gas analysis

Quantitative anal. — what is in a certain material

steel — % C

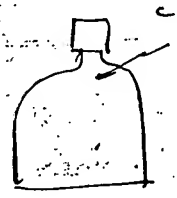
stainless — % Ni - Cr

air — % carbon monoxide

whiskey — % fusel oil

I Concen. of materials

Sulfuric acid



commercial acid
94 % by wt.
1.84 Sp. Gr.

1000 gallons of 50 % by wt.

How many ~~gallons~~ lbs. of strong acid
→ 1000 gallons of 50 % by wt.

$40 \times 0.92 = 36.8$ g. NaOH

$\frac{36.8}{40} = 0.920$ N as NaOH.

$\frac{40 \times 0.02}{53} = \frac{0.015 \text{ N as } Na_2CO_3}{0.935 \text{ N}}$

1 cc

 of H_2O = 1 gm. at 4°C

1 cc of H_2SO_4 Density = wt/cc. at a definite temp.

 = 1.84 gms. at 60°F

1000 gals. × 378.5 = 3,785,000 cc

cc's/gal.

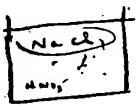
378

3,785,000 × 1.526 = gms. of 50% acid

gms of 50% acid × 0.50 = gms. pure H_2SO_4

Exam #1
PCM
6/16/52

Gravimetric analysis



gm./cc
gm./gallon

$NaCl + AgNO_3 \longrightarrow AgCl + NaNO_3$

1 mole

AgCl

23
35
58

Gravimetric Factors

$\frac{NaCl}{AgCl} \times$ wt of AgCl = wt of NaCl

3.2067 gm

$\frac{\text{Sought}}{\text{Weighed}} \times$ amt weighed = amt. sought.

NaCl : wt of NaCl = AgCl : wt of AgCl

NaCl | AgCl = wt of NaCl : wt of AgCl

$\frac{NaCl}{AgCl} \times$ wt of AgCl = wt of NaCl

6/6/50

SO_4^{2-}

$Na_2SO_4 + BaCl_2 \xrightarrow{HNO_3} \underset{\text{white ppt}}{BaSO_4} + 2NaCl$ 1.5264.

Gravimetric Factor

$\frac{\text{formula weight}}{\text{weighed}} \times \text{amt weighed} = \text{amt sought.}$

Gravimetric factor

$\frac{Na_2SO_4}{BaSO_4} \times 1.5264 \text{ gm.}$

0.6086

$142.1 \times 1.5264 = 233.4$ = amt. Na_2SO_4

1 gm of a mixture | amt of NaCl / SO_4 ratio

NaCl

Tomato Paste

$AgNO_3$

acidified HNO_3

⑥

0.0070 amt. Nail

~~Sample~~ Weight × amt/weight = amt/sample

Sample Factor = 0.0070 amt. = amt. Nail

0.408 × 0.0070 amt. = 0.0029 amt. Nail

0.408
0.0070
0.002856

% by wt of Nail

amt. Nail / 100 amt. paste

lbs. Nail / 100 lbs. paste

0.29 / 1 × 100 = 0.29 % Nail by wt.

Amt. Found / Amt. Weighed × 100 = % by Wt

0.29 lbs. Nail

454 × 0.29 =

4

6/6/15

Ordinary operations of quant. chemical analysis.

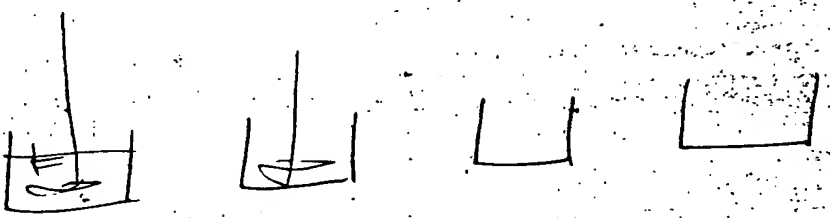
1. Solution

NaCl 3 gm/100 cc

$NaSO_4$

a. see Handbook for solubilities.

$KMnO_4$



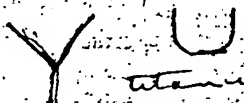
3 gm/100 cc

.01

.02/liter

2. Precip. – see directions from book

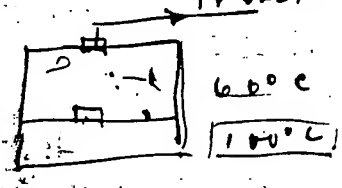
3. Filtration – Fuel



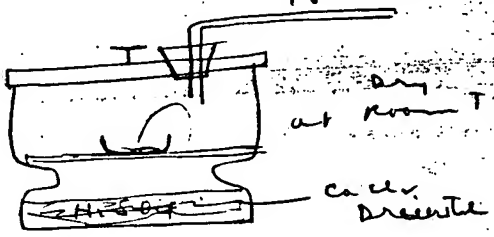
titanium crucible

6/6/

Drying of Precipitate



Vac Drying then Desiccation



overnight

Reweighing

Volumetric analysis

Vol. anal. is easier + faster than grav. anal.

Pipet
Buret
VH. Flask
analytical balance

Primary std

0.1 N Dichromate $Na_2Cr_2O_7$

0.1 N NaOH

acidimetry + alkalimetry

0.5 conc. $NaClO_3$ (dry + purified)

always react with a definite amount of acid (HCl, H_2SO_4)

Base 0.2 NaOH

Benzoic acid (U.S. Bureau of Stds)
K acid phthalate (in molec. wt)
Constant boiling HCl.

Oxidation + Reduction stds

0.1 N Iodine } use $K_2Cr_2O_7$ as std
0.1 N Thiosulfate }

$Ce_2(SO_4)_3$ Use in Stds

$KMnO_4$ 0.1 N { Ferrous ammonium sulfate
Dry $Na_2C_2O_4$ (sodium oxalate)

Normality of solns.

a 1 N soln of anything (acid, base, oxidizing agent, reducing agent) contains 1 eq. wt. in grams of the reacting substance.

∴, to know how to make up a 1 N soln, the reaction must be known before the Normality can be classified.

$$HCl + NaOH \rightarrow H_2O + NaCl$$

36.5 gm/l → 1 N soln

$$H_2SO_4 + 2NaOH \rightarrow 2H_2O + Na_2SO_4$$

98

1 N of NaOH is still 40 gm/l.

$$\frac{1}{2}H_2SO_4 + NaOH \rightarrow H_2O + \frac{1}{2}Na_2SO_4$$

49

$\frac{98}{2} = 49$ gm H_2SO_4/liter

$$H_3PO_4 + 3NaOH \rightarrow 3H_2O + Na_3PO_4$$

3

1 c.c. of any 1 N acid = 1 c.c. of any 1 N base

HAc
HCl
H_2SO_4
oxalic acid
Ca(OH)$_2$
Ba(OH)$_2$
KOH
NaOH
T.E.A.

6/6/50

(6)

Basic Rule for Vol. analysis

$cc_s \times N_s \times$ meq = amt V

reacting soln. → std

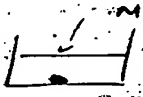
= milliequivalent wt

= wt of std substance in 1 cc of a 1 N soln.

= soln of acid N? — HCl

Suppose — (0.5 am. Na_2CO_3)

0.5000



30.26 cc to titrate — What is N of acid

$cc_s \times N_s \times$ meq = amt V

$30.26 \times N_s = 0.053$ = 0.5000

$Na_2CO_3 + 2HCl \rightarrow 2NaCl + CO_2 + H_2O$

$\frac{1}{2}Na_2CO_3 + HCl \rightarrow \frac{1}{2}NaCl + \frac{1}{2}CO_2 + \frac{1}{2}H_2O$

$\frac{\text{Mwt } Na_2CO_3}{2} = \frac{106}{2} = 53$ am. / l → 1 N soln.

Na_2CO_3

1 cc = $\frac{53}{1000} = 0.053$ am.

#1 6/6/50

Some $\times$ 0.653 = $N_s \times$ 0.500

1.603 $\times N_s$ = 0.5000

$$N_s = \frac{0.5000}{1.603}$$

N_s = 0.3119 N

Equivalent Volumes of different acids.

HCl

HCl 0.1026 N

0.0832 N

25 cc

Do you have enough for all 10 titrations

10 determ

What must be found out, is how many cc of 0.0832 N HCl for each titration

If it takes 25 cc of 0.1026 N to do the job, then it should take more than 25 cc of 0.0832 N to do the same work

For $\frac{0.1026}{0.0832} \times 25 = 30.87$ cc / titration

Then,

for 10 titrations

30.87 $\times$ 10 = 308.7 cc

PS, m 6/6/50

~~boob × 0.055~~ , N_s = 0.500

1.603 × N_s = 0.5000

$$N_s = \frac{0.5000}{1.603}$$

N_s = 0.3119 N

Equivalent Volumes of different solns:

HCl

0.1026 N

25 cc

HCl

0.0832 N

Do you have enough for all 10 titrations

10 determ

What must be found out, is how many cc of 0.0832 N HCl for each titration

If it takes 25 cc of 0.1026 N to do the job, then it should take more than 25 cc of 0.0832 N to do the same work

So, $\frac{0.1026}{0.0832} \times 25 = 30.87$ cc / titration

Then,

for 10 titrations

30.87 × 10 = 308.7 cc

6/6/70

(12)

NaOH 0.2030 N

32.62 cc.

KOH

12.50 cc

What is N of KOH

∴ KOH is stronger & N of KOH must be > N of NaOH

$$\frac{32.62}{12.50} \times 0.2030 = 0.52 \text{ N KOH}$$

You have a 0.4186 N acid H_2SO_4

It takes ~ 8.31 cc for a titration

This figure is so small, that any error in reading → a > error in results

So, you want to dilute the acid so that it will take at least 40 cc for the same titration. What then will be the N of the acid?

$$\frac{8.31}{40.0} \times 0.4186 = 0.0868 \text{ N}$$

$V_1 N_1 = V_2 N_2$

$\frac{8.31}{40} \cdot 0.4186 = 40 \cdot N_2$

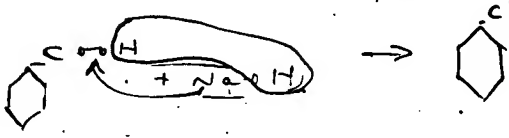
Exp #1 PSM 6/4/13

(13)

You have an approx. 0.2 N KOH
you want to titrate it with benzoic acid
You should use between 20 & 40 cc for
the titration (to cut down any error
in the method or the reading of the burette).
What wt. of benzoic acid should you
use?

cc's × N's × mil. eq. = gms of

40 × 0.2 × 0.1221 = gm. of COOH



So, gm. equiv. of COOH = benzoic acid = 122.1 g./lit

= $\frac{122.1}{1000}$ = 0.1221 g. = mil. eq.

So, gms = 0.977

0.9 1.0

0.8

0.7

Expt. (13)
6/61

(14)

making up Std. Solns. of acids

0.1 N H_2SO_4 — how prepare?

Need

49 gms./l → 1 N H_2SO_4

So, 4.9 gms./l → 0.1 N H_2SO_4

Take regular strong (conc.) H_2SO_4

on label

1.84 Sp. Gr.

94 - 95 %

cc acid × Sp. Gr. × % pure acid = gms pure acid

1 × 1.84 × 0.95 = 1.75 gms H_2SO_4/cc

we want 4.9 gms.

So, $\frac{4.9}{1.75}$ = 2.8 cc acid/l

→ 0.1 N Soln.

Usually 3 cc is used with a pipet due to acid clinging to the side.

For HCl, say a 0.5 N Soln.

HCl is gas.

Hydrochloric acid is the gas dissolved in H_2O.

1.19 Sp. Gr.

38 %

Exp #1
(PSP)
6/6/70

(15)

Need:

36.5 gms. HCl / l → 1 N

3.65 gms. HCl / l → 0.1 N

or

36.5 × 0.5 = 18.25 gms. / l → 0.5 N

1 cc of HCl (conc.) =

cc acid × sp. gr. × % acid = gms. pure acid

1 × 1.19 × 0.38 = 0.414 gms. pure HCl / cc

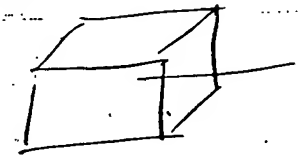
So, for 0.5 N

gms. HCl / l of 0.5 N

$\frac{18.25}{0.414}$ = 43.1 cc.

gms. pure HCl / cc

$\frac{\text{gms.}}{\frac{\text{gms}}{\text{cc}}}$ = gms × $\frac{\text{cc}}{\text{gms}}$ = cc



18.25 gms. pure HCl Needed

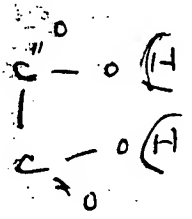
? cc. Needed

0.414 gms. pure HCl = 1 cc

6/6/15

oxalic acid in acidimetry & alkalimetry

$H_2C_2O_4 \cdot 2H_2O$ (2H-O) varies



white crystals

1 N Soln. = $\frac{H_2C_2O_4}{2}$

$= \frac{126.05}{2} = 63$ gm./l

→ 1 N

Making Ltp. Std Solns of Bases.

Usually give weight approx. amount rapidly (as they take on H_2O)

NaOH 40 gm./l → 1 N

KOH 56 gm./l → 1 N

NaOH & KOH contain Na_2CO_3 & they give elaborate methods for getting rid of it & excluding the carbonate

In fact, some people prefer to use $Ba(OH)_2$ because the carbonate is insoluble. But for most work it can be neglected

Oxidation & Reduction Vol. Technique

1. must know equiv. (just as for acidimetry & alkalimetry)

2. must have primary Std.

3. must know how Starch color. ion.

$Na_2S_2O_3$

↳ used in literally a thousand reactions where the final step is always the titration of liberated

$2Na_2S_2O_3 + I_2 \rightarrow$ $Na_2S_4O_6 + 2NaI$

sodium tetrathionate — colorless

$I = Na_2S_2O_3$ or $Na_2S_2O_3 \cdot 5H_2O$

↓ 126 — 248 gm/l → 1N

— 24.8 gm/l → 0.1 N

Starch I^- → blue color

Problems

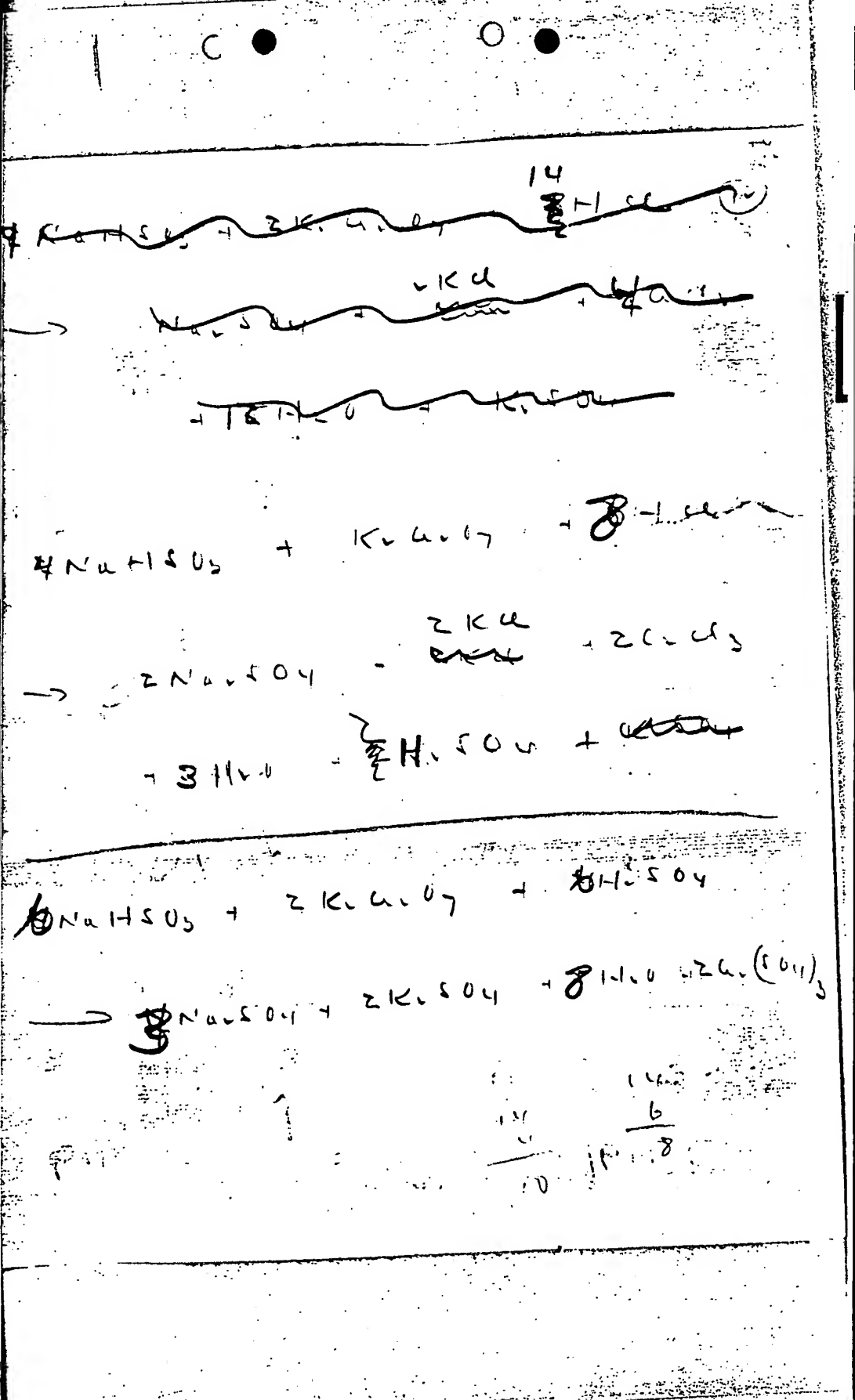
p. 81	# 151
p. 82	# 151
p. 83	# 162
p. 83	# 164

$6NaHSO_3 + 2K_2Cr_2O_7 + 16HCl \rightarrow$

$3Na_2SO_4 + 3H_2SO_4 + 4KCl + 8H_2O$

$+ 4CrCl_3$

6/6/50



#3

Received June 6, 1950

Joseph Field
(Title of Contributor)

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(Name of Sp... (Seal)

To be known as (?)

Description of V 3 Manila Folder marked Photographic Evidence

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Photocopies

Nicotinic Acid

#3

06/6/50

ALLYL CYANIDE

$$2CuSO_4 + 5NaCN \rightarrow 2CuCN + (CN)_2 + 2Na_2SO_4$$

$$CH_2{=}CHCH_2Br + CuCN \rightarrow CH_2{=}CHCH_2{-}CN + CuBr$$

Submitted by J. S. Buckleton and S. F. Harris.
Checked by Reuben Q. Thompson and Lee Irvin Smith.

1. Procedure

(A). Preparation of Cuprous Cyanide.—(Note 1) In a 5-l. round-bottomed flask fitted with a stopper carrying a mechanical stirrer, a separatory funnel, and a gas exit tube leading to a good hood (Note 2) is placed a solution of 650 g. (2.6 moles) of crystallized copper sulfate in 1 l. of water. The flask is surrounded by an oil bath and heated to about 80°. The stirrer is started and a solution of 255 g. (5.2 moles) of sodium cyanide (Note 3) in 650 cc. of water is added from the separatory funnel over a period of about one-half hour. Then the mixture is boiled until no more cyanogen gas is evolved. This requires about five to ten minutes.

The cuprous cyanide, which begins to separate as a light tan precipitate at room temperature after a few cubic centimeters of the cyanide solution has been added, is allowed to settle and the solution is decanted. The precipitate is filtered, then washed with water (1 l.) and finally with alcohol (500 cc.) and ether (300 cc.). After drying at 110° for about thirty-six hours, the product weighs 200–210 g. (85–90 per cent of the theoretical amount).

(B). Allyl Cyanide.—In a 5-l. round-bottomed flask fitted with a condenser (Note 4) and a mechanical stirrer are placed 220 g. (1.83 moles) of allyl bromide (Note 5) and 170–175 g. (1.9 moles) of dry cuprous cyanide (Note 6). The mixture is heated in a water bath and the stirrer rotated slowly by hand until the reaction starts (about fifteen to thirty minutes). When the reaction does begin it becomes vigorous, and the heating bath must be replaced by a cooling mixture of ice and water in order to avoid loss of product through the condenser. After the vigorous reaction has subsided, the water bath is replaced, the mechanical stirrer is started, and the mixture is heated until no more allyl bromide refluxes. This requires about one hour.

The condenser is then set for distillation and the allyl cyanide is distilled from the flask, which is heated in an oil bath with stirring (Notes 7 and 8). Upon redistillation, the allyl cyanide is pure and boils

BIOTIN AND PARA-AMINOBENZOIC ACID AS GROWTH FACTORS FOR THE ACETONE-BUTANOL ORGANISM, CLOSTRIDIUM ACETOBUTYLICUM

Sir:

Rubbo and Gillespie [Rubbo and Gillespie, *Nature*, 146, 838 (1940)] have recently reported that p-aminobenzoic acid (p. a. b.) is a growth factor for nine strains of *Cl. acetobutylicum*. They state that it is the only factor required by the organism. We are unable to confirm this conclusion.

In a previous paper [Oxford, Lampen and Peterson, *Biochem. J.*, 34, 1588 (1940)] we reported that *Cl. acetobutylicum* on a medium of glucose, asparagine and Speakman's salts requires the addition of biotin and of an unidentified factor from yeast. The basal was identical with that of Rubbo and Gillespie except that 0.11% of salts was added instead of the 1.2% which they used. Asparagine-ammonium sulfate or ammonium phosphate were also used as nitrogen sources.

In later experiments we have found that p. a. b. will replace the yeast factor. This activity together with the close agreement between the properties of the two make it evident that the active substance in our earlier preparations was either p. a. b. or some equivalent compound. However, growth does not occur on the addition of p. a. b. alone to the basal medium. If biotin is added also, growth is optimal. This result has been obtained with strains S9 from our collection and nos. 824 and 862 of the American Type Culture Collection. No. 862 is one of the strains used by Rubbo and Gillespie. All strains required both biotin and p. a. b. Table I illustrates the effect of the two factors on the S9 strain.

TABLE I

EFFECT OF BIOTIN AND P. A. B. ON *CL. ACETOBUTYLICUM* S9 ([illegible] Collection)

Biotin (γ/cc.)	p. a. b. (γ/cc.)	Growth value
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00001	[illegible]	[illegible]
.00002	[illegible]	[illegible]
.00005	[illegible]	[illegible]
.00010	[illegible]	[illegible]
.00020	[illegible]	[illegible]

Growth was determined by measuring the turbidity in an Evelyn photoelectric colorimeter. The biotin employed was the crystalline methyl ester obtained through the generous coöperation of Professor V. du Vigneaud.

Our only explanation of the discrepancy between our findings and those of Rubbo and Gillespie is that the natural constituents of their medium may have contained biotin. We have found that some grades of glucose contain appreciable quantities of this factor.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN
J. O. LAMPEN
W. H. PETERSON

RECEIVED JULY 24, 1941

THE PREPARATION OF NICOTINIC ACID FROM PYRIDINE

Sir:

The recent report by Gilman and Spatz [Gilman and Spatz, THIS JOURNAL, 63, 1553 (1941)] on the preparation of 3-cyanoquinoline from 3-bromoquinoline and the hydrolysis of the cyano compound to the corresponding acid prompts the publication of a parallel synthesis in the pyridine series on which we have been working. Since 3-bromopyridine may be prepared by the direct bromination of pyridine [Englert and McElvain, *ibid.*, 51, 863 (1929); Wibaut, et al., *Rec. trav. chim.*, 51, 381 (1932)], the synthesis now reported makes nicotinic acid readily available from pyridine. The following is the procedure by which 3-cyanopyridine (nicotinonitrile) was prepared. To 6.25 g. (1 mol) of 3-bromopyridine in a Claisen flask set for vacuum distillation was added 5.3 g. (1.5 mol) of cuprous cyanide [Organic Syntheses, Coll. Vol. I, p. 38]. The mixture, which warmed spontaneously, was heated to 165–170° in an oil-bath for one hour. The resulting black viscous reaction product was then heated under about 30 mm. pressure with a smoky burner flame until no more volatile material came over. The nitrile that distilled over solidified in the receiver. After recrystallization from ligroin (b. p. 60–68°) the yield of product that melted at 49–50° [Fischer, *Ber.*, 15, 63 (1882)] amounted to 2.1 g. (50%).

3-Cyanopyridine is readily converted to nicotinic acid by hydrolysis. The following procedure was found to be satisfactory. A solution of 3.6 g. of 3-cyanopyridine and 4 g. of sodium hydroxide in 60 ml. of 70% alcohol was refluxed

...tions were. The extract was then removed ... R. D. McAllister and R. R. Rochm, *J. Biol. Chem.*, ... evaporation and the residue dissolved in 25 cc. ... 113, 315 (1936)] and a growth curve may be illus- ... water. This aqueous solution after shaking by ... trated as follows.

... twice carefully extracted with ether. The combined ...

Days fed	Body weight, grams
0	9.7
7	10.0
14	13.8
21	24.6
28	41.5
35	62.0

... ether extracts, after drying over anhydrous ... The concentrated substance stimulates the growth ... of rats to 2.5 g. (40%) and melted at 21° sharp. ... of *L. arabicus* and *L. casei* with similar condi- ... tions and dosages.

... Chemistry, ... *L. casei* stimulates *L. casei* under the same ... University of Texas, ... conditions as the factor concentrated by Snell and ... Austin, Texas, June 24, 1941 ... Peterson [E. E. Snell and W. H. Peterson, *J. Bact.*, 39, 273 (1940)] and recently reported to be ...

... CONCENTRATION OF FOLIC ACID ...

... Concentrates from *L. casei* cultures ... Considerable phosphorus content in the ... folic acid while the element is absent from ... considerable portion of this material was ... acid. Another marked difference lies in ... precipitated by phosphotungstic acid and ... specific activity, folic acid an ... by adsorption on fuller's earth. ... purest form obtained produces approximately ... The material contains carbohydrate and ... growth in our microbiological ... nitrogen and a considerable weight of ash. ... test at a level of 0.00012 γ/ml. while this effect ... 400 has been determined by extension of the ... Streptococcus lactis R under the testing con- ... assay and possesses high physiological activity ... ditions, at about 0.014 γ/ml. ... This substance, which has certain chemical ... It was obtained that the sub- ... properties in common with folic acid, has ... stance may have vitamin-like properties for ani- ... been found in a number of ... mals, as a series of rats on a control diet the ... sources, and is widespread in the biological ... average gain was 64 g. per 21 days. Five rats of ... kingdom. Yeast, liver and green leaves ... same litter gained an average of 71.5 g. (cor- ... (is especially abundant in green leaves of many ... rections for sex differences) when 40 γ of folic ... plants, such as spinach, lettuce, alfalfa and ... acid concentrate per rat per day were given. ... clover) are the richest natural sources ... Lack of the factor in the diet of young rats ... obtained when working on ... caused profound changes in the intestinal ... *Lactobacillus casei* (Latin, *casei*, cheese). ... mucosa. ... Many common ... [Received, June 24, 1941] ... substances, ...

... ADDITION REACTION OF ALKALI-TREATED ... SILK, INVOLVING A NEW SYNTHESIS OF ... HISTIDINE

... Chemistry, ... Chemistry, ... University of Texas, ... University of Texas, ... Austin, Texas, ... Austin, Texas, ... [Received, June 24, 1941] ...

of perbromide bromine gave a 40% yield of 3,5-dibromopyridine but none of the 3-bromopyridine. A mixture of pyridine hydrobromide and this perbromide gave a 35% yield of 3-bromopyridine and a 10% yield of the dibromopyridine. The greatest yields of brominated pyridines were obtained when the lower perbromide was heated. In this case 36–38% yields of 3-bromopyridine and 30–36% yields of 3,5-dibromopyridine were obtained. The yield calculations were made on the basis of the bromine used in the preparation of the perbromides.

Experimental

Pyridine Hydrobromide Perbromide (47% Perbromide Bromine).—To a warm (60–65°) solution of 160 g. (1 mole) of pyridine hydrobromide in 240 g. of glacial acetic acid in a large beaker, a solution of 160 g. (1 mole) of bromine in 160 g. of acetic acid was added. The resulting solution was stirred thoroughly by hand and then allowed to cool. After two to three hours there was deposited a mass of large, orange-red, needle-shaped crystals. They were filtered off and dried in a desiccator. They were quite stable and when dry melted at 129–134°. The yield was 300–310 g. (95–97% based on the formation of $C_5H_5N \cdot HBr \cdot Br_2$). These crystals were analyzed for perbromide bromine by the method of Trowbridge and Dicks[7] and found to contain 47.0% of such bromine.

Pyridine Hydrobromide Perbromide (39.7% Perbromide Bromine).—This perbromide was prepared in exactly the same manner as the one described above except that 80 g. (0.5 mole) of bromine in 80 g. of acetic acid was added to the warm solution of 160 g. of pyridine hydrobromide in acetic acid. The crystals obtained melted at 101–103° and the yield averaged 205 g. Analysis showed 39.7% of perbromide bromine. There was no appreciable change in weight in either of these perbromides when they were allowed to stand in a vacuum desiccator over sulfuric acid for several days.

3-Bromopyridine and 3,5-Dibromopyridine.—These products were prepared in better yields from the lower perbromide. The perbromide containing 39.7% of bromine as perbromide as obtained in the preparation described above was mixed with the residue left by the evaporation of the acetic acid mother liquors. The weight of this mixture amounted to approximately the sum of the weights of pyridine hydrobromide and bromine (that is, 240 g.) used in the preparation of the perbromide. This solid mixture was heated in a round-bottomed flask under a reflux condenser in a sodium nitrate–potassium nitrate bath that was maintained at 230–250°. The solid melted at about 100° and as the liquid reached the bath temperature there was a vigorous evolution of hydrogen bromide. The evolution of hydrogen bromide gradually subsided and at the end of six to eight hours had practically ceased. During the reaction there was considerable condensation of crystals of 3,5-dibromopyridine on the cooler parts of the flask and in the reflux condenser. When the evolution of hydrogen bromide had ceased, the reaction mixture was steam distilled until no more crystals of 3,5-dibromopyridine appeared in the condenser. The distillate consisted of an acid solution and suspension of 3,5-dibromopyridine which was completely precipitated out by the addition of alkali. The precipitate was filtered off and recrystallized from alcohol. The yield was 18–23 g. of a product that melted at 110–111°. The residue left in the flask after the removal of the 3,5-dibromopyridine by steam distillation was made strongly alkaline with sodium hydroxide and again steam distilled. The distillate consisted of water, pyridine and 3-bromopyridine and as it first came over was clear, but as the proportion of water increased it became turbid and when about 250 cc. of distillate had been collected, a layer of 3-bromopyridine and some pyridine was present in the receiver. This layer was

Diehl[1] were unable to obtain a definite compound from bromine and pyridine in aqueous solution but in chloroform solution they obtained a compound which appeared to have the formula $C_5H_5N \cdot Br_4$. On standing this tetrabromide lost bromine and passed into a compound which analysis showed to have the formula $C_5H_5N \cdot Br_3$. Barthe[2] obtained from pyridine and bromine a perbromide to which he assigned the formula $C_5H_5N \cdot Br$. Trowbridge and Diehl also prepared perbromides of salts of pyridine. By passing bromine into an aqueous solution of pyridine hydrobromide they obtained two perbromides, one of which contained 41.95% of bromine and the other 53.06% of bromine that was present as perbromide bromine. The latter compound melted at 93° and the formula $C_5H_5N \cdot HBr \cdot Br$ was assigned to it. The perbromide containing 41.95% of perbromide bromine was assumed to be a mixture of $C_5H_5N \cdot HBr \cdot Br_2$ and $C_5H_5N \cdot HBr \cdot Br$. These investigators also prepared a perbromide in aqueous solution to which they assigned the formula $C_5H_5N \cdot HBr \cdot Br_2 \cdot H_2O$. It melted at 118–120° and contained 67.96% of perbromide bromine.

In the work which is reported here it was found that glacial acetic acid was a much better solvent than water for the preparation of these perbromides because both reactants (bromine and pyridine hydrobromide) were quite soluble in this medium and the perbromides which were formed, while very soluble in warm acetic acid, were quite insoluble in the cold acid. From one mole of bromine and one mole of pyridine hydrobromide in acetic acid solution there was obtained a perbromide that melted at 122–124°. The yield was 95–97% of the theoretical based on the formation of $C_5H_5N \cdot HBr \cdot Br_2$. While this formula requires 50% perbromide bromine content, there was found only 47% of perbromide bromine in the product that melted at 122–124°.

One mole of pyridine hydrobromide and one-half mole of bromine in glacial acetic acid solution gave a perbromide that melted at 101–103° and had 39.7% of perbromide bromine. The perbromide bromine in the compound of the formula $C_5H_5N \cdot HBr \cdot Br$ amounts to 33.3%. The authors are not able as yet to assign satisfactory formulas to these perbromides but it is hoped that further work will throw some light on this subject.

An attempt was made to use pyridine hydrochloride instead of pyridine hydrobromide for the preparation of these perbromides but it was found that the yields from the hydrochloride were considerably lower than those from the hydrobromide and that the perbromides of pyridine hydrochloride were very deliquescent and quite difficult to handle.

When these perbromides were heated at 230–250° under a reflux condenser, there was a vigorous evolution of hydrogen bromide with the formation of 3-bromo- and 3,5-dibromopyridine. The perbromide containing 47%

[1] Trowbridge and Diehl, THIS JOURNAL, 19, 658 (1897).
[2] Barthe, *Compt. rend.*, 145, 73 (1907).

separated, dried with solid sodium hydroxide and fractionated. The fraction that boiled at 160–175° amounted to 29–31 g. On redistillation practically all of this fraction boiled at 168–173°. The yield of the dibromopyridine was 30–36% of the theoretical and that of the 3-bromopyridine 36–38% of the theoretical based on the bromine used in the preparation of the perbromide.

The separation of 3,5-dibromopyridine from 3-bromopyridine by steam distillation of the former from acid solution was originally used by Ciamician and Silber[2] and is fairly satisfactory but not complete. There appears to be some of the di-substitution product left with the monobromopyridine even after prolonged steam distillation, and in the final distillation of the latter compound a small amount of the dibromopyridine usually crystallizes in the condenser.

When the perbromide of higher bromine content was heated under similar conditions, a 40% yield of the dibromopyridine was obtained but none of the 3-bromopyridine was found. It was thought that dilution of this higher perbromide with pyridine hydrobromide might increase the yield of the mono-substituted product but several runs in which 2 moles of pyridine hydrobromide was mixed with 1 mole of the higher perbromide gave an average of 10% yield of 3-bromopyridine and 30% yield of the 3,5-dibromopyridine.

Summary

A convenient method of brominating pyridine to 3-bromopyridine and 3,5-dibromopyridine has been described. It consists of the preparation of a perbromide of pyridine hydrobromide in glacial acetic acid solution and the transformation of this perbromide by heat into the bromopyridines.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

SYNTHETIC GLYCERIDES. I. PREPARATION AND MELTING POINTS OF GLYCERIDES OF KNOWN CONSTITUTION[1]

BY H. P. AVERILL, J. N. ROCHE AND C. G. KING

RECEIVED OCTOBER 22, 1928 PUBLISHED MARCH 6, 1929

The isolation of pure triglycerides from natural fats and oils is an uncertain and laborious process because of the difficulty of complete separation. Even when pure triglycerides have apparently been obtained satisfactory evidence is not available to indicate which of the possible isomers has been found. It was thought that progress could best be made through the synthesis of glycerides of known constitution and the study of their chemical and physical properties. Data thus obtained will be valuable in the study of the components of naturally occurring fats and oils.

It seemed probable that definite relationships might be found between certain physical properties of the fats and their molecular structure if sufficient data were available to warrant conclusions. The three sets of isomers (only one having fatty acids) prepared by Fischer[2] indicated that

[1] This paper is based upon a part of the theses submitted by H. P. Averill and J. N. Roche to the Graduate School, University of Pittsburgh, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] E. Fischer, *Ber.*, **53**, 1631 (1920).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE BROMINATION OF PYRIDINE[1]

BY S. MARY ELIZABETH ENGLERT AND S. M. MCELVAIN

RECEIVED OCTOBER 22, 1928 PUBLISHED MARCH 6, 1929

The preparation of 3-bromopyridine and 3,5-dibromopyridine by the direct bromination of pyridine has long been known as a rather difficult reaction to carry out. Nevertheless, it appears to be the simplest method available for the preparation of these particular bromopyridines in quantity. Hofmann[2] was able to prepare 3,5-dibromopyridine by heating pyridine dibromide, $C_5H_5N \cdot Br_2$, in a sealed tube for one hour at 200°. He obtained the same product by heating pyridine hydrochloride and bromine together in a sealed tube. In neither reaction did he report the formation of 3-bromopyridine. Later, Ciamician and Silber[3] prepared 3-bromopyridine along with 3,5-dibromopyridine by heating pyridine hydrochloride and bromine in a sealed tube as Hofmann had done. They, however, heated their mixture for a longer time (twenty-four hours) and at a higher temperature (210–220°). Their combined yield of the mono- and dibromopyridines was only 21% of the theoretical. Blau[4] reported an improvement over the earlier sealed-tube methods, which consisted essentially of passing a mixture of bromine and carbon dioxide through molten pyridine hydrochloride. By this procedure the combined yield of the mono- and dibromopyridines was 42% of the theoretical.

This communication reports what seems to be a distinct improvement over all of the older methods of bromination of pyridine. The procedure consists of heating a perbromide of pyridine hydrobromide at 230–250° under ordinary pressure until the evolution of hydrogen bromide ceases.

There appears to be considerable variation in the composition of the perbromides of pyridine and pyridine salts as reported in the literature. Anderson[5] and Hofmann[2] treated pyridine and pyridine hydrochloride in aqueous solution with bromine and obtained crystalline precipitates which showed fair stability and to which they assigned the formula $C_5H_5N \cdot Br_2$. Grimaux[6] treated pure pyridine with bromine and obtained a compound that crystallized in thin, red plates and melted at 126°. To this compound he assigned the formula $(C_5H_5N \cdot Br_2)_7HBr$. Trowbridge and

[1] A portion of the thesis submitted by S. Mary Elizabeth Englert to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Master of Science.

[2] Hofmann, *Ber.*, 12, 988 (1879).

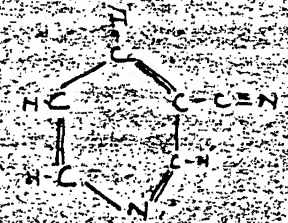
[3] Ciamician and Silber, *Ber.*, 18, 722 (1885).

[4] Blau, *Monatsh.*, 10, 372 (1889).

[5] Anderson, *Ann.*, 105, 341 (1858).

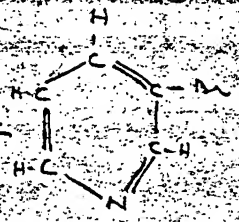
[6] Grimaux, *Compt. rend.*, 95, 85 (1882).

Exp. 6

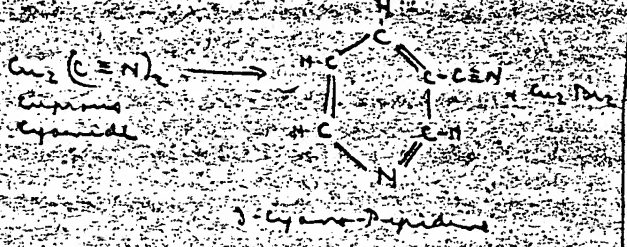


3-Cyano-Pyridine

1. Reaction



3-Bromo-Pyridine



3-Cyano-Pyridine

2. Reactants

3-Bromo-Pyridine

Cuprous Cyanide

3. Reagents

None

4. Yield

50 %

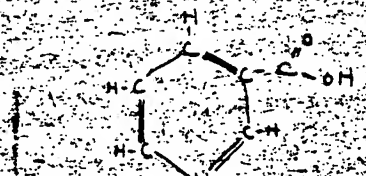
5. Unit operations

A₁ - B₂ - C₁ - D₁ - H₁ - J₁ - L₁ - N₁ - P₄

6. Solvents

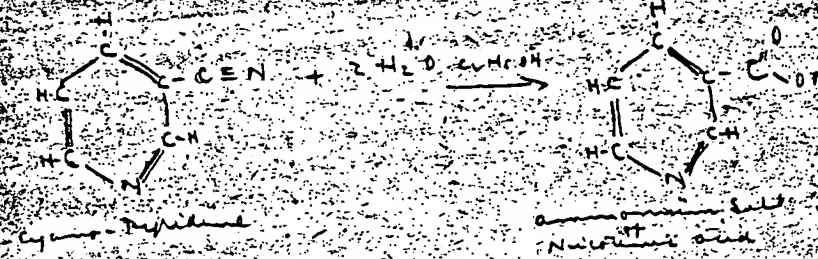
Petroleum Ether

Exp 3

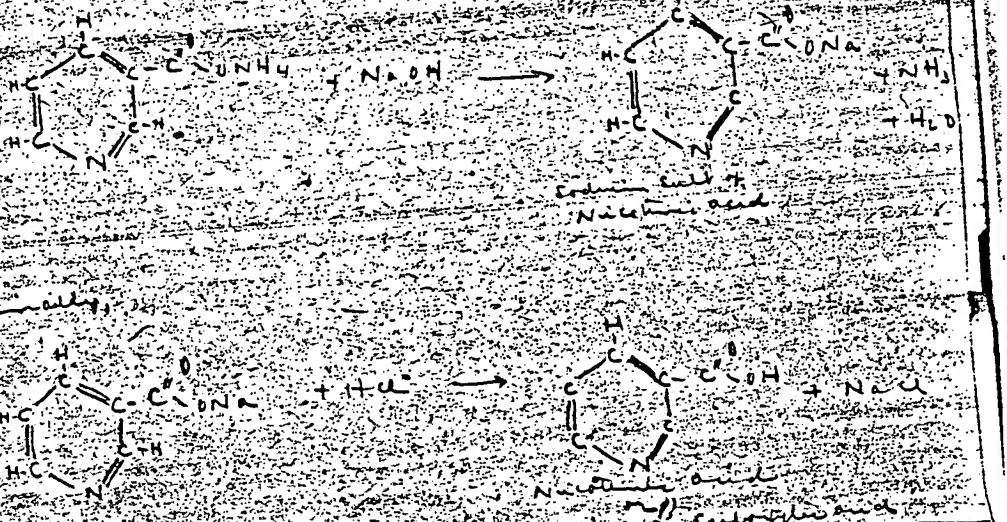


Nicotinic acid
or
Pyridine-3-carboxylic acid

Reactions



3-cyano-Pyridine



Example 1 (cont'd)

2. Reactants

3. Cyanuric chloride
Water

3. Reagents

Sodium Hydroxide
Hydrochloric acid

Yield

90%

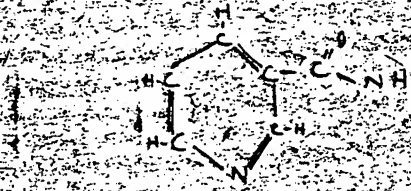
5. Unit operations

$A_2 - B_2 - C_2 - D_1 - W_1 - W_3 - L_1 - N_1 - P_4$

6. Solvents

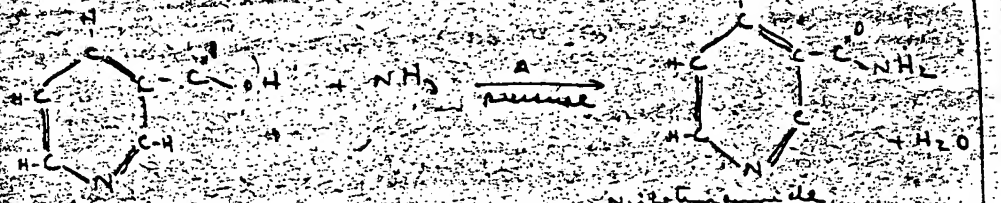
None

Step 4



Nicotinamide
or
Pyridine-3-carboxylic acid amide

1. Reaction



Nicotinic acid
or
Pyridine-3-carboxylic acid

Nicotinamide
or
Pyridine-3-carboxylic acid-amide

2. Reactants

Pyridine-3-carboxylic acid (nicotinic acid)

ammonia (gas)

3. Reagents

None

4. Yield

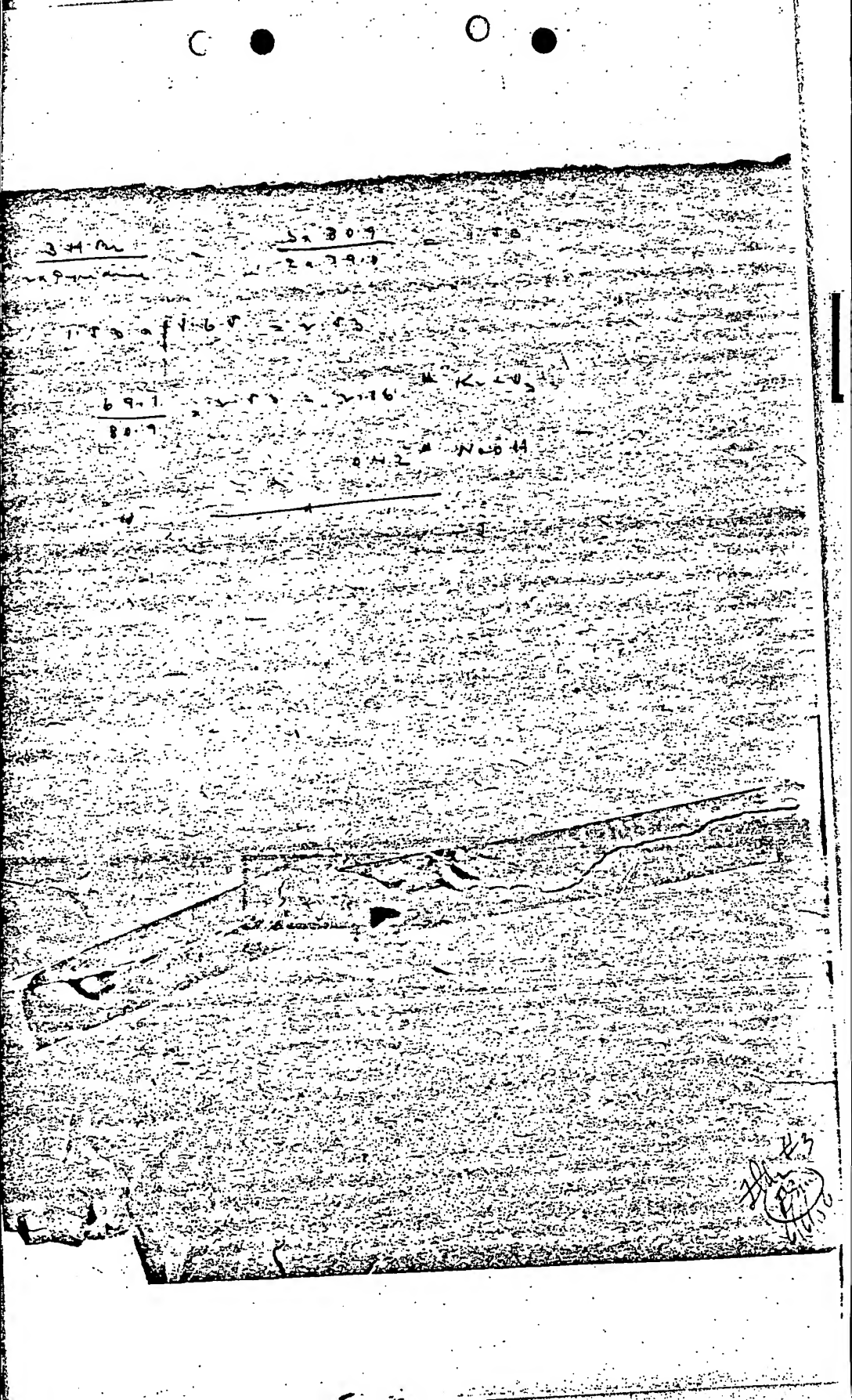
75 %

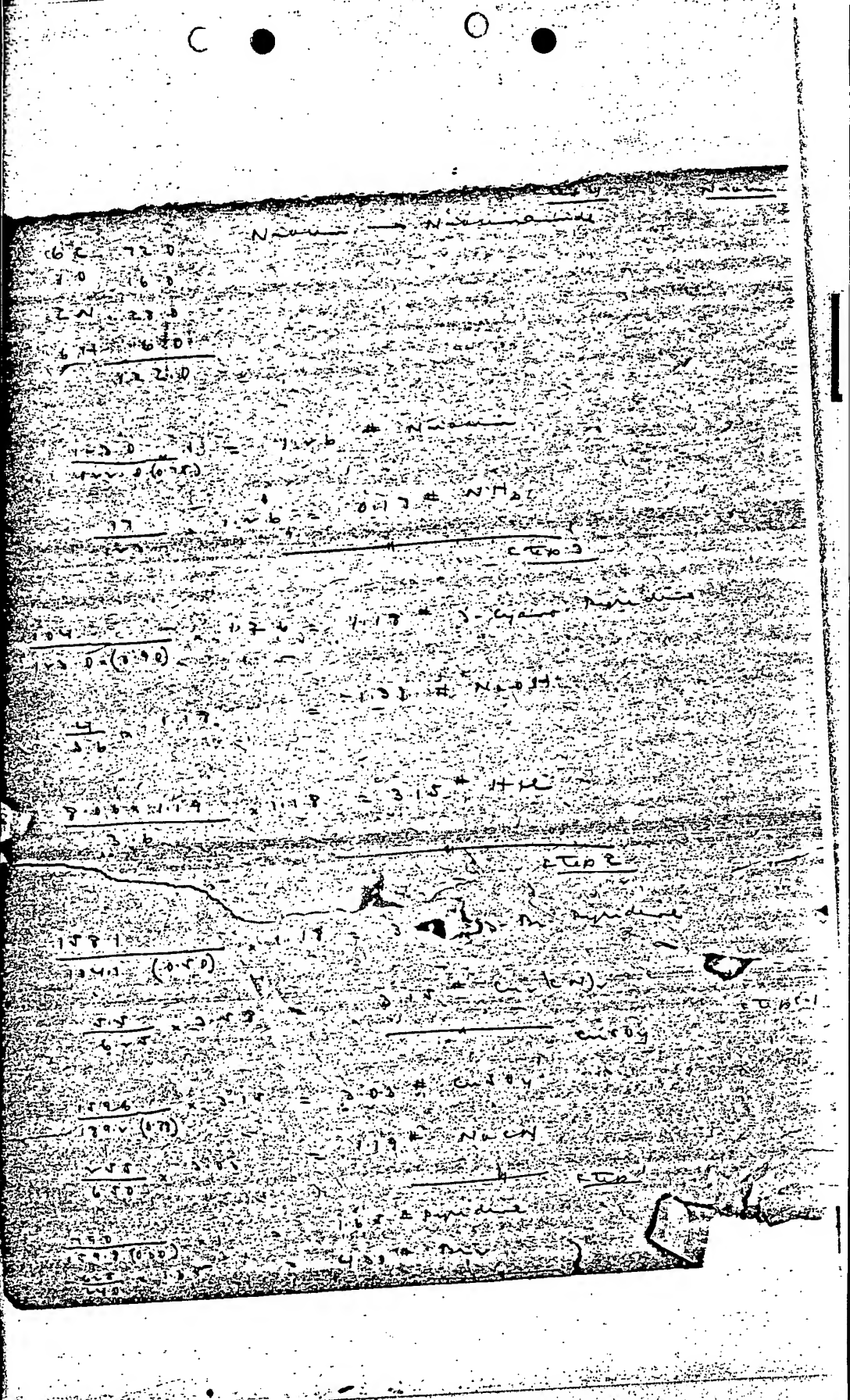
5. Time of reaction

A3 - D1 - C11 - D1 - I1 - J4 - Z1 - N1 - P4

6. Solvents

None





Step 1

Step 1-1

Step 2

Step 3

Step 4

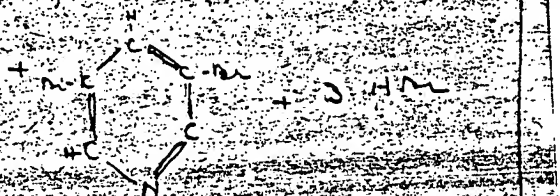
Pyridine	1.65
	4.30
Bromine	0.37
K_2CO_3	2.16
NaOH	1.73
$CuSO_4 \cdot 5H_2O$	0.93
NaCN	1.19
	0.15
NH_3 (gas)	0.17

Eqpl

3-Bromo-Pyridine

Reaction

3-Bromo-Pyridine



3,5-Dibromo-Pyridine

2. Reactants

Pyridine

Bromine

3. Reagents

Concentrated Oleum

Potassium Carbonate

Potassium Hydroxide

4. Solvent

5. Temperature

$A_2 - D_1 - L_2 - b_1 - H_1 - J_4 - P_1$

6. Time

Cool mixture (0°C)

Copper Sulfate

Exp C-1

$Cu_2(C\equiv N)_2$

Cuprous cyanide

Reaction

$2\,CuSO_4 + 4\,NaC\equiv N \longrightarrow Cu_2(C\equiv N)_2 + (CN)_2 + 2Na_2SO_4$

Cuprous cyanide

2. Reactants

Copper Sulfate

Sodium cyanide

3. Reagents

None

4. Apparatus

P-7-V

5. Manipulations

$A_1 - B_2 - C_3 - I_1 - J_4 - L_1 - N_1 - P_1$

6. Solvents

Ethyl alcohol (95%)

Ethyl Ether

Filter the Nitrotime and crystals

Wash the crystals once with 4 cc of water at 5°C

Dissolve the Nitrotime and in 40 cc of hot

H2O

Evaporate the solution to half its

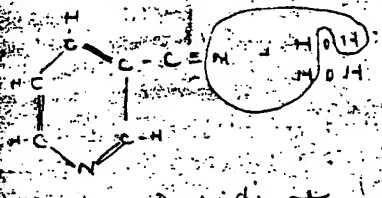
Cool the solution to 5°C. The Nitrotime and

crystals precipitate

Filter the Nitrotime and crystals

Dry the crystals

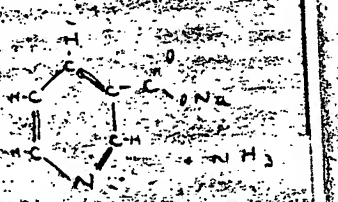
Yield 90%

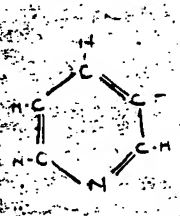


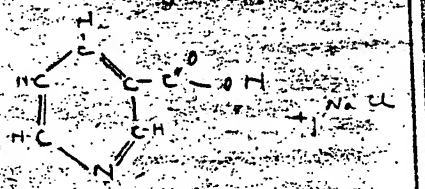
3-Cyano-pyridine

M.W. 104.0

m.p. 49° - 50°C







Nicotinic acid

or

Pyridine-3-carboxylic acid

M.W. 123.0

m.p. 234°-236°C

1. Dissolve { 3.6 gms. of 3-Cyano-pyridine / 4 gms. of NaOH } in 40 c.c. of 70% alcohol

2. Reflux the solution (at temp 90°C (194°F)) for 3 hrs.

3. Evaporate the solution to dryness.

4. Dissolve the residue in 25 c.c. of H2O.

5. Cool the solution to 0°C

6. Exactly neutralize the solution with 50% H2SO4

7. Nicotinic acid crystals out. Yield 70%

Yield 83.0

$2\ CuSO_4 + 4\ NaCN \longrightarrow 2\ Cu(CN)_2 + (CN)_2 + 2\ Na_2SO_4$

mw 159.2 49.0 179.2

Dissolve { 650.0 gms of $CuSO_4 \cdot 5H_2O$; 4000 cc of H_2O

Heat the solution to 80°C (176°F)

add { 255 gms of NaCN dissolved in 650 cc of H_2O } under agitation

and boil a ½ hr period.

Cool the solution for 10 hrs to 25°C.

Cyanogen gas is evolved.

Filter the crystals from the supernatant liquid

Wash the crystals with 1000 cc (total) of water

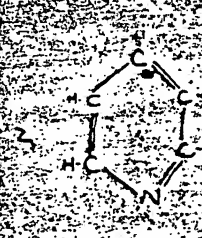
Wash the crystals with 500 cc (total) of alcohol

Wash the crystals with 300 cc (total) of ether

Dry the crystals at 110°C for 36 hrs (?)

230°F

Yield 50%



3-Bromo-pyridine
M.W. 158.9
b.p. 173°C
(760 mm)

+ $Cu_2(CN)_2$
cuprous cyanide
M.W. 139.2

3-cyano-pyridine
M.W. 104.1
m.p. 49°-50°C

Reactants { To 6.25 cc of 3-Bromo-pyridine add 5.5 cc of $Cu_2(CN)_2$

Heat the mixture cautiously until the mixture becomes uniformly molten. Continue heating to 168°C (334°F) for 1 hour. A black, viscous reaction product results.

Distill the black reaction product at 440°C (752°F) and 2 mm Hg pressure. The desired 3-cyano-pyridine and other volatile matter comes over with the vapor. Solidify the 3-cyano-pyridine in the receiver.

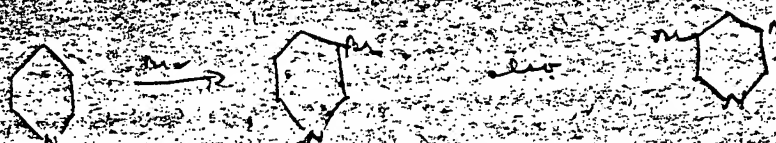
Dissolve the cyano-pyridine in 10 cc of petroleum ether.

Decolorize the solution to 4°C.

Cool the solution to 5°C to obtain crystals of cyano-pyridine.

Filter the crystals

Dry the crystals



4

Date Received June 6, 1950

Joseph Held
(Name of Contributor)

6823 Kimball St, Phila
(Address of Contributor)

Robert Shaster
(Name of Signer if Group)

To Be Returned

Description of Item(s) French folder marked Pantheon Award

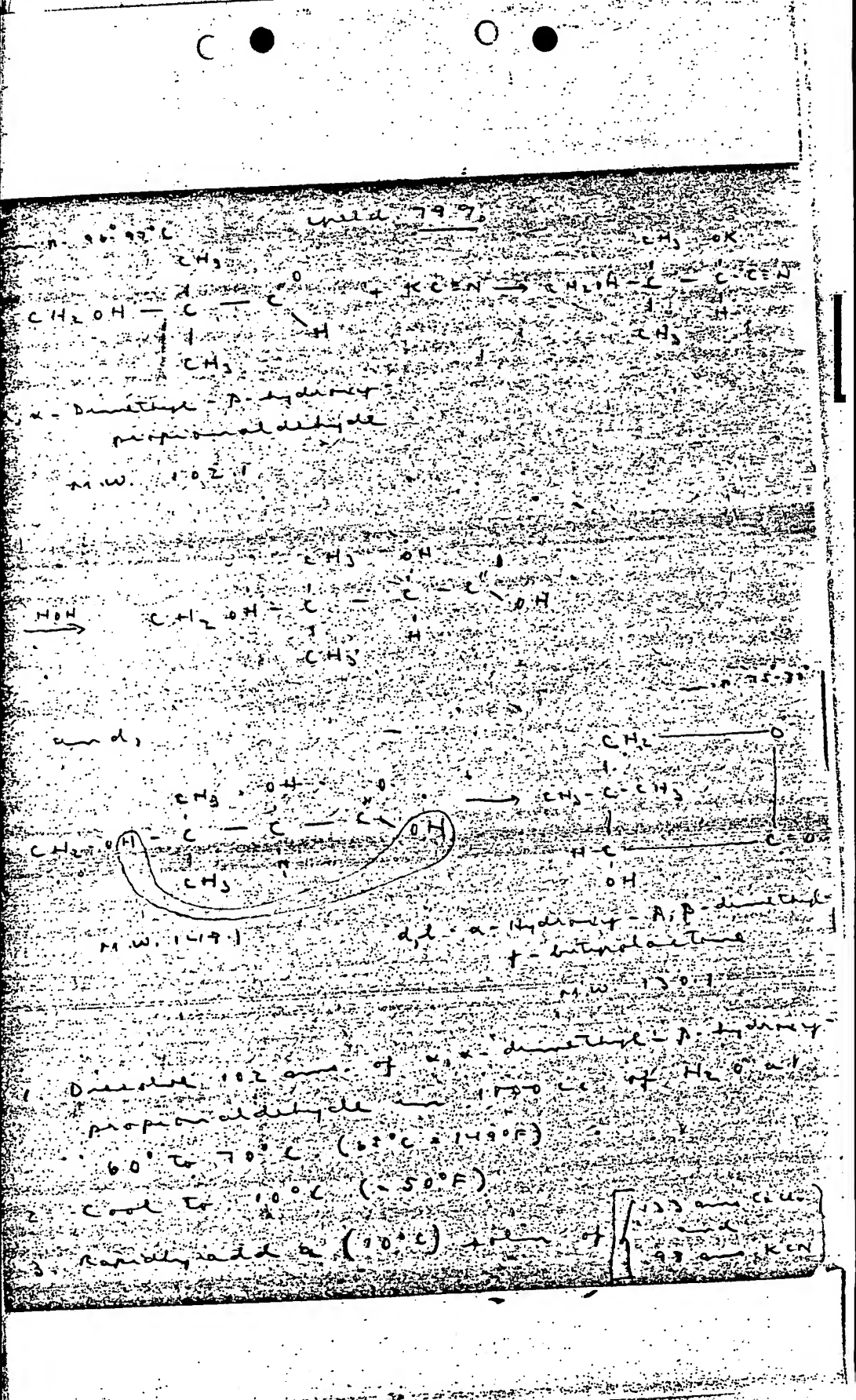
File No. 65-4347-18-14

Exp. 36

at 75°-76°C in toluene. The solution is
crystallized immediately
10. The crystals are dissolved in alcohol
and the alcohol evaporated to ½ volume
11. The soln is cooled → purified crystals
12. The crystals are filtered
13. The crystals are dried at 60°C (140°F)
under vacuum

Wild 797

m.p. 90-92°C



1. Dissolve 102 gms. of α-α-dimethyl-β-hydroxy propionaldehyde in 1700 cc of H_2O at 60° to 70°C (65°C = 149°F)
2. Cool to 10°C (~50°F)
3. Rapidly add to (10°C) the mixture of 123 gms. CuSO4 and 99 gms. KCN

... $CaCl_2 \cdot 4H_2O$] and let stand for 18 hrs.
at 2-5° C with occasional agitation.

3. This must be done in a CO_2-free atmosphere.

4. Heat the solution to 75° C (167° F)

5. add 15 l. of $Ca(OH)_2$ - $2H_2O$

6. Filter off the $CaCO_3$

7. Evaporate the filtrate to a syrup under vacuum. As much of the water as possible should be removed.

8. Extract the residue with 1000 cc (Total) of anhydrous acetone.

9. Filter out the insoluble material.

10. Concentrate the acetone solution to a syrup (say 120 cc) under vacuum.

11. Take up the syrup in 1000 cc of dry acetone.

12. Evaporate the acetone.

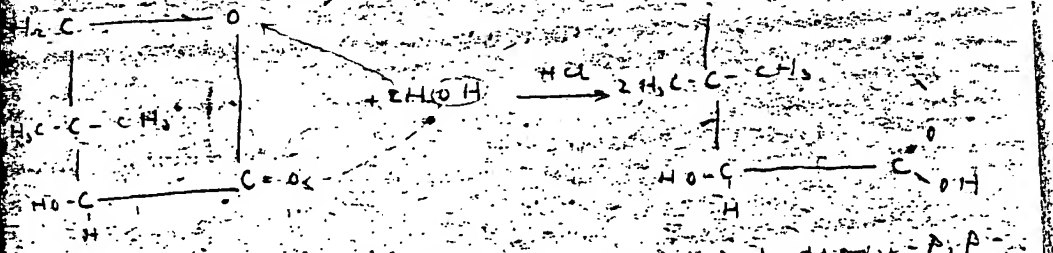
13. Distill (fractionate) the residue at 122-130° C and 18 mm. vacuum. An oil is obtained which crystallizes immediately to a glass in the receiver.

14. Dissolve the lactone in 200 cc of cold (5° C) ethyl ether.

15. add cold (5° C) petroleum ether till the

a thin, uniform cloudy suspension of the
3 thin) clusters of fine colorless needle crystals
2. Filter the crystals
3. Wash twice with 200 cc portions of 50%
petroleum ether
4. Dry the crystals

Yield 3.1 [illegible]



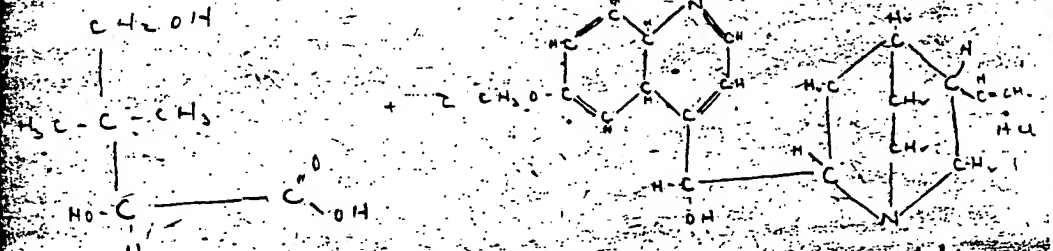
α-Hydroxy-β,β-dimethyl-γ-butyrolactone

MW 130.1

α,γ-Dihydroxy-β,β-dimethyl butyric acid

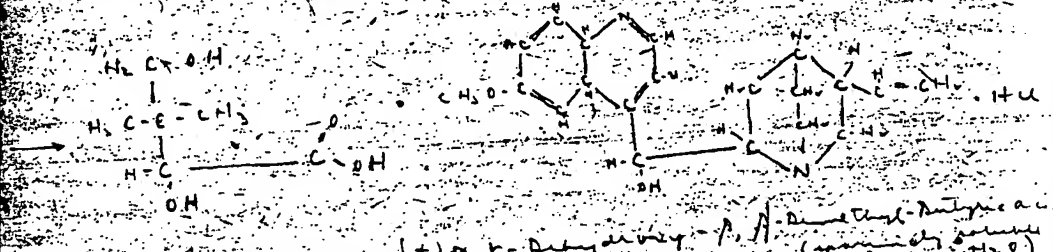
MW 148.1

and



Quinine hydrochloride

MW 396.9

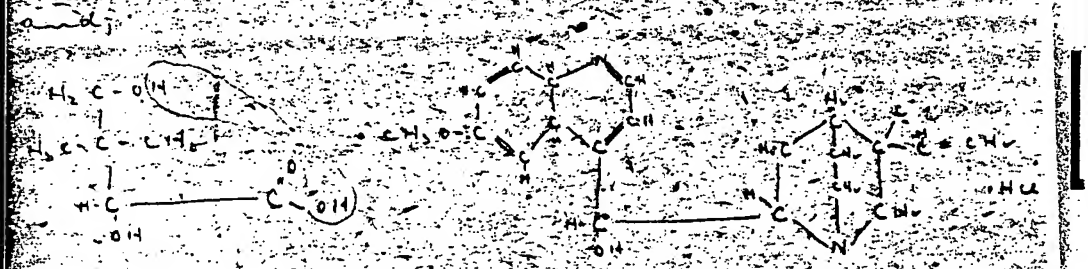


Quinine salt of (+) α,γ-Dihydroxy-β,β-Dimethyl-Butyric acid

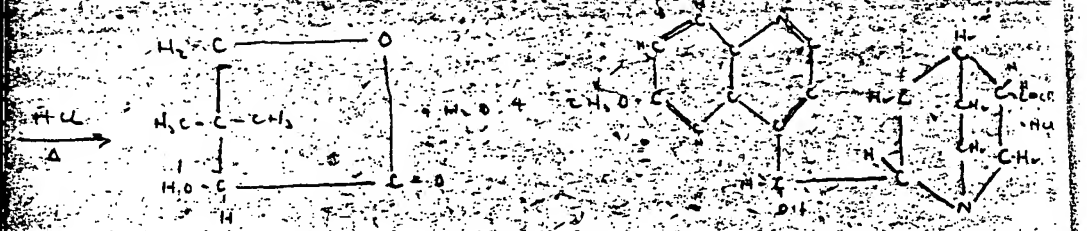
(monohydrate)

Quinine salt of (+) α,γ-Dihydroxy-β,β-Dimethyl-Butyric

and



Quinine, salt of (+) α, β-Dihydroxy-β, β-dimethyl-butyric acid



(−) α-Hydroxy-β, β-dimethyl-γ-butyrolactone

Quinine hydroxide

M.W. 130.1

1. 27 gms. of racemic lactone are dissolved in 48.5 cc. of H_2O.
2. 46 cc. of 0.872 N. NaOH (7.13 gms. = 43 cc.) are added.
3. The solution is heated to 35°C. (95°F.)
4. The solution is cooled to 20°C. (68°F.)
5. The excess alkali (0.72 gms.) is neutralized with 7.2 cc. of 2 f H_2SO_4 (≈ 1 cc. of 36% H_2SO_4).
6. The solution is diluted to 400 cc. and aqueous is heated to 35°.

3.2 gm of guanidine hydrochloride are added to the hot soln with stirring. Separation of the crystallized guanidine salt of (+)-α,β-dihydroxy-β,β-dimethyl-butyric acid commences after only a small part of the guanidine has been added.

2. The soln and crystals are chilled to 0°C and kept at 0°C for 12 hrs.

3. The crystals are filtered off.

4. The crystals are washed twice with ice-cold water.

5. The crystals are dried at 60°C. (yield 32 gm)

6. The mother liquors from 3 and 4 are concentrated to dryness in vacuo. A further crystallization of the guanidine (+) salt takes place.

7. The soln is cooled to 20°C and the added crystals filtered.

8. The added crystals are washed twice with H₂O.

9. The added crystals are dried at 60°C.

10. The two crops from 7 and 9 are combined.

11. The combined crops are dissolved in 34 cc of 2.5 N HCl (= 17 cc of 5 N HCl).

19. The solution is heated at 100°C for 2.0 hours.

20. The solution is cooled to 20°C.

21. The solution is continuously extracted for 11 hrs with ether.

22. The ether solution is evaporated to dryness.

23. 50 c.c. of 95% Ethanol + 5 c.c of Benzol are added.

24. The Ethanol-Benzol-H_2O azeotrope is distilled off and the remainder of the ethanol is also driven over to leave a dry residue.

25. The residue is dissolved in a solution of 10 cc of Benzol + 40 cc of Petroleum Ether b.p. 40°C

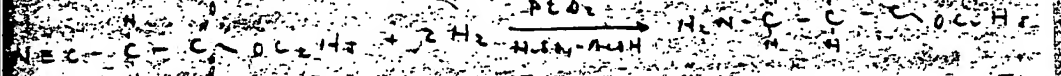
26. The solution is evaporated to 20 c.c.

27. The solution is cooled to 10°C to yield a crop of crystals.

28. The crystals are filtered.

29. The crystals are dried in air.

Wild 7497



cyano-ethyl acetate

M.W. 113.1

m.p. 13°C

β-diazo cinnamic ester

M.W. 147.1

m.p. 58°C

Reactants { 5 gms cyano-ethyl acetate
400 cc acetic acid (420 gms.)
10 cc conc. H-SO4 (18.4 gms.) }

1. Mix the reactants and add 2 gms of PtO2 hydrogenating catalyst
2. Pass in H2 under 40 atmospheres pressure and agitation at 22°C (72°F) for 1 hr. (The theoretical uptake of H2 is 1.06 gms)
3. The catalyst is filtered off
4. The acetic acid is distilled off under 12 mms vacuum
5. add 7 gms of H2O at 0°C and keep the mix at this temperature
6. add strong caustic (approx 40%) dropwise under cooling and with stirring agitation until a pH of 8.0 is reached (the theoretical amount should require 14 cc of 40% caustic soda of NaOH)

8. Add 250 cm. of anhydrous K_2CO_3 (approx 250 gm) portions a stiff paste results

9. Wash thick paste with 500 cc portions of ether

10. To the combined ether washings add anhydrous K_2CO_3 (approx 100 gm) to dry the ether soln

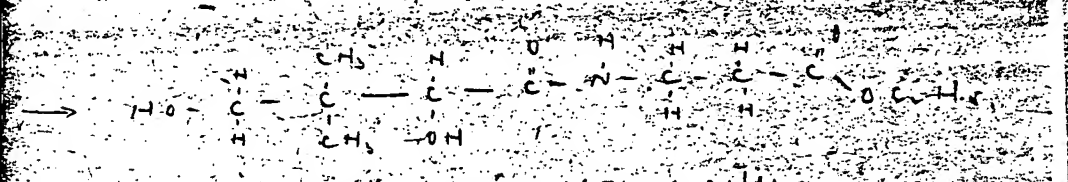
11. Filter off the K_2CO_3

12. Distill off the ether under vacuum and then distill the 7-dimethyl ether also under vacuum

Yield 6.1.70

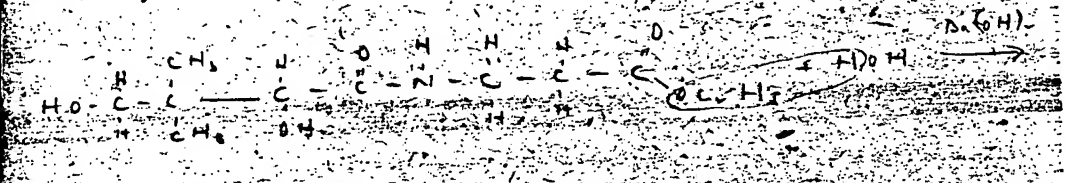
(-) α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

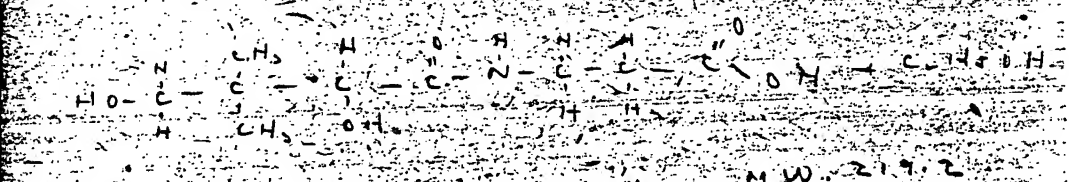
M.W. 130.1



(+) Pantothenic acid, Ethyl ester

and,





(+) Pantothenic acid.

M.W. 219.2

or

(+) - α, γ - Dihydroxy - β, β - Dimethyl - Butyric - β - alanide

mix 3.75 gms. of (-) α - Hydroxy - β, β - Dimethyl γ - Butyrolactone with 7.5 gms. of β - alanine Ethyl ester

1. Heat the mixture for 2 hrs. at 71°C (159°F).
2. Cool the mixture to 25°C (77°F).
4. Add 300 cc of 0.45 N $Ba(OH)_2$ (2.5 gm $Ba(OH)_2 \cdot 3H_2O$ made up to 300 cc).
5. React at 25°C for 2½ hrs.
6. Add 22.6 cc of 6N H_2SO_4 (= 3.3 cc of 96% H_2SO_4 made up to 22.6 cc) to precipitate the barium.
7. Centrifuge out the $BaSO_4$.
8. Wash twice with 100 cc portions of H_2O.
9. Adjust the pH to 5.5 with pyridine.
11. Evaporate the solution to dryness in vacuum at 25°C to yield a colorless syrup.
11. Dry the syrup in a high vacuum over P_2O_5.
12. Dissolve the syrup in 20 cc of MeOH.
13. Add 12.00 cc of acetone slowly with vigorous agitation.
14. Cool to 0°C and keep till the oil crystallizes and the supernatant liquid is clear.
15. Filter at 0°C.
16. Dissolve the collected crystals in cold

in 20 cc of MeOH.

17. add 120 cc of acetone slowly with vigorous agitation.

18. cool to 0°C and keep till the precipitate

19. Filter at 0°C

20. Dissolve the acetone insoluble material in 20 cc of MeOH.

21. add 120 cc of acetone slowly with vigorous agitation.

22. cool to 0°C and keep till the precipitate

23. Filter at 0°C

24. Combine the acetone-methanol liquors from 15, 19 and 23 and evaporate to dryness in vacuum at 25°C to yield a pale yellow oil.

25. Dissolve the oil in 40 cc of H2O

26. Neutralize to pH 7.5 with 0.9 N NaOH.

27. Continuously extract the liquid with ether for 18 hrs. to remove a small amount of unchanged lactone

28. add 1.6 N H2SO4 to ppt the Ba ion

29. Filter off the BaSO4

30. Wash the cake twice with 40 cc portions of H2O

31. The aqueous liquors from 29 and 30, are combined and pyridine is added to adjust the pH to 5.5.

32. The solution is evaporated to dryness under vacuum at 25°C. a pale yellow oil remains as product.

33. The oil is dried under high vacuum over H_2SO_4.

34. The dry oil is extracted twice with 450 cc portions of acetone after vigorous agitation with the acetone.

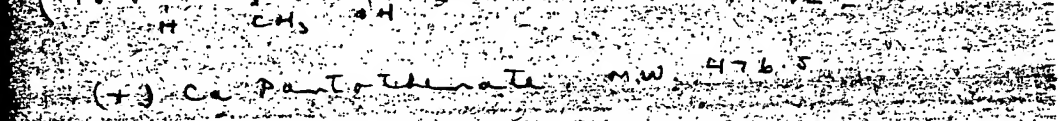
35. The combined extracts were cooled to 0°C and kept at this temperature till the supernatant liquid had cleared. A small amount of crystals of D-glucuronic lactone

36. Filter off the D-glucuronic crystals

37. Evaporate the acetone soln. to dryness in vacuum to yield a pale yellow syrup.

38. Dry the syrup in high vacuum at 40°C over H_2SO_4.

(+) Pantothenic acid
MW 219.2



(+) Ca Pantothenate MW 476.5

or

Ca salt of (+)-α, γ-Dihydroxy-β, β-Dimethyl-butyryl-β-alanine

1. 3.5 gms of (+) Pantothenic acid are dissolved in 20 cc. of H_2O
2. add 1.0 gms $CaCO_3$ (~0.7 gms min.) until dissolution
3. Filter off the excess $CaCO_3$
4. Wash the cake twice with 5 cc portions of water
5. Evaporate the combined filtrate and washings under vacuum to yield a hard colorless glass
6. Dissolve the glass in about 15 cc of MeOH (use the minimum amount of MeOH) add small amount of insoluble material formed
7. Filter off the insoluble material

8. add the $NaBH_4$ solution slowly with vigorous agitation to about 500 ml of ether. A colorless microcrystalline powder forms.

9. Filter off the precipitate

10. Dry the crystals at 78°C (173°F) in vacuum.

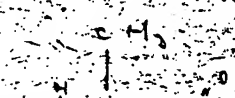
Cinnamaldehyde - Trans-cinnamic aldehyde

Prep by oxidation of cinnamyl alcohol with benzoic acid

Cinnamyl alcohol

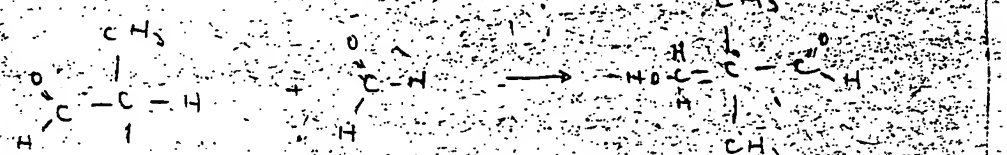
Prep by partial distillation of storax with soda

Isobutyraldehyde



α, α - Dimethyl - β - Hydroxy - Propionaldehyde

1. Reaction



Isobutyraldehyde — Formaldehyde — α, α - Dimethyl - β - Hydroxy - propionaldehyde

2. Reactants

Isobutyraldehyde

Formaldehyde (47.7% Formalin)

3. Reagents

K_2CO_3

4. Yield

86 %

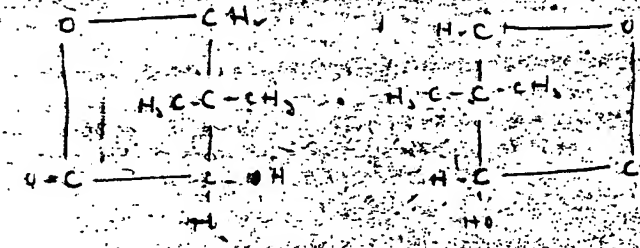
5. Unit operations

$A_5 - B_2 - C_3 - D_2 - E_1 - H_1 - I_1 - J_2 - L_1 - N_2 - P_2$

6. Solvents

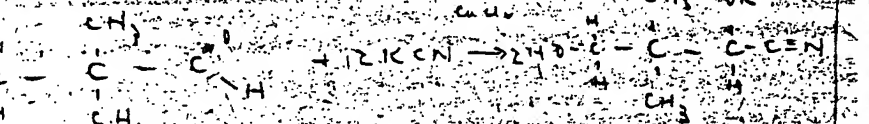
Ethyl Ether

Ethyl alcohol



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

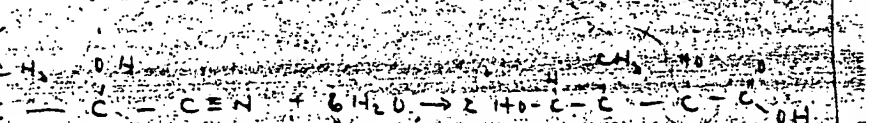
1. Reaction



α, α - Dimethyl - β - Hydroxy - propionaldehyde

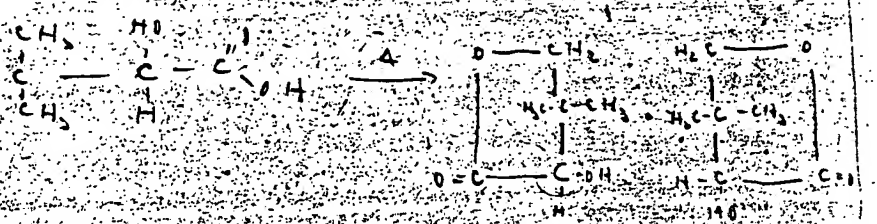
KCN addition product of α, α - Dimethyl - β - Hydroxy - propionaldehyde

and



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyric acid

Chem.



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

2. Reactants

α,α-Dimethyl-β-Hydroxy-Propionaldehyde
potassium cyanide
Water

3. Reagents

calcium chloride
oxalic acid

4. Yield

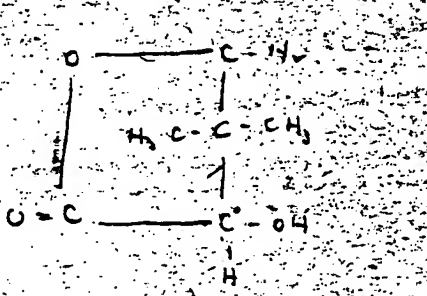
79%

5. Unit operations

A_{10} - B_9 - L_3 - D_3 - E_1 - H_1 - I_1 - J_6 - L_2 - N_1 - P_8

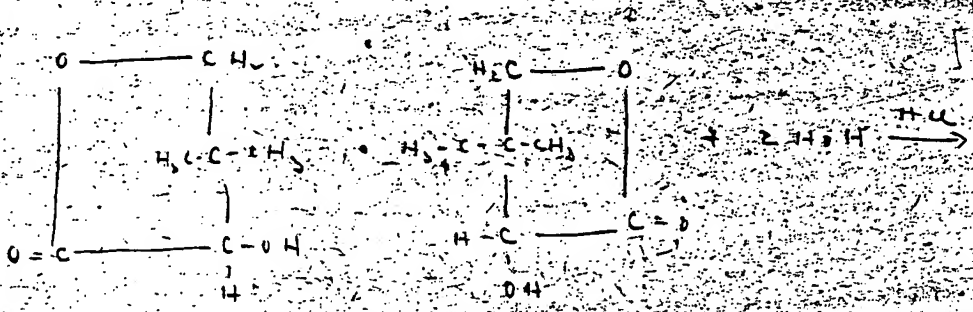
6. Solvents

acetone
Ethyl Ether
Petroleum Ether

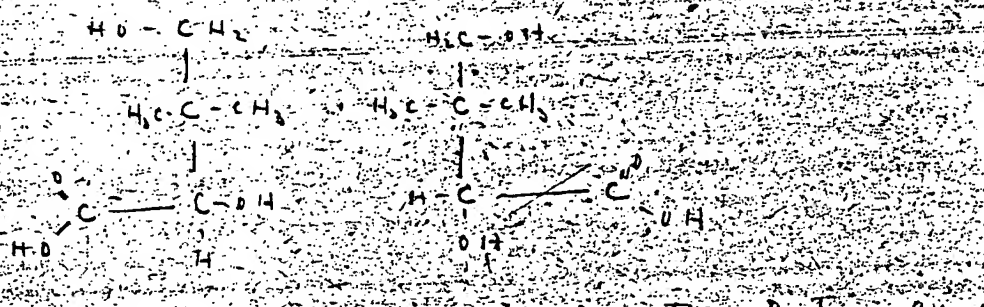


(-) α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

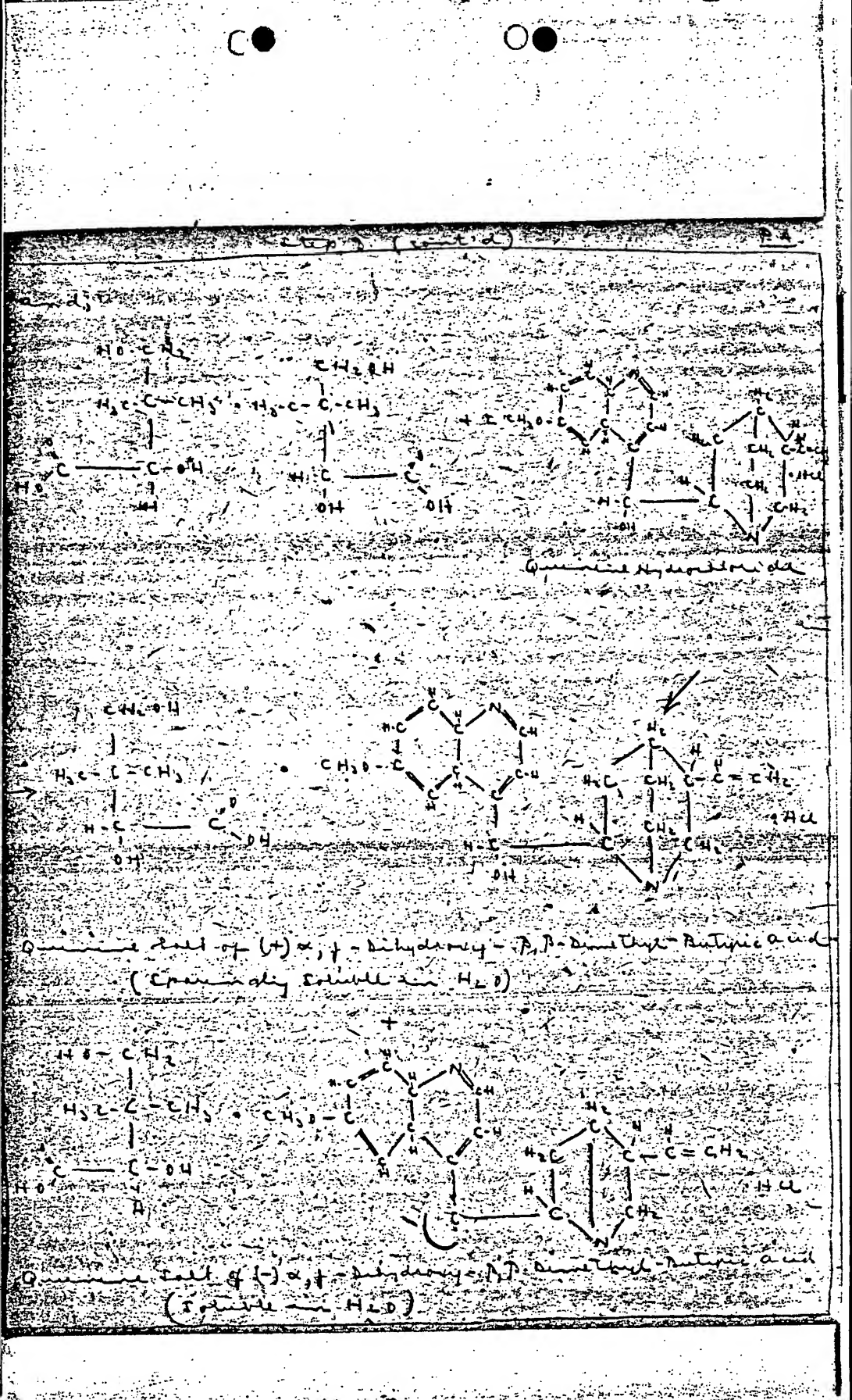
1. Reaction



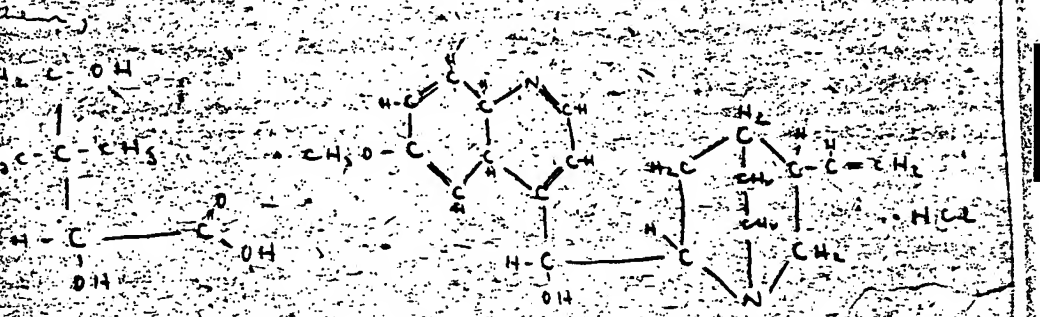
d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone



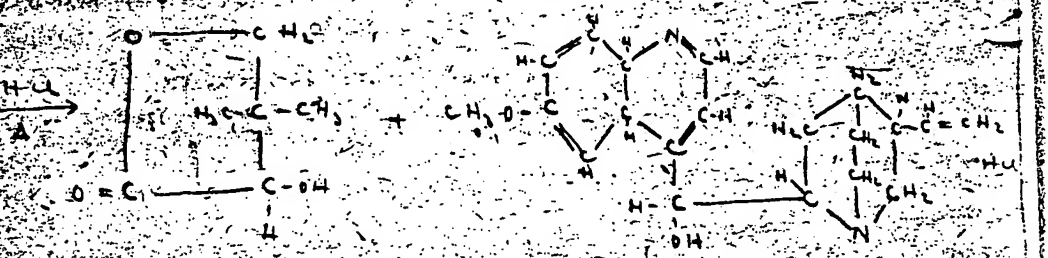
d, l - α, γ - Dihydroxy - β, β - Dimethyl - Butyric acid



Example 3 (contd.)



Quinine salt of (±) α,γ-Dihydroxy-β,β-Dimethyl-Butyric acid-γ-



(±) α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

2. Reactants

dl-α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

Quinine Hydrochloride

3. Reactants

Solution Hydrochloride

Hydrochloric acid

4. Yield

37%

5. Other operations

A - B - C - D - E - H - I - R

J - L - N - P - S

6. Solvents

Cold Ether

Cold alcohol

Benzene

Step P-1

monochloro acetic acid

$N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - OC_2H_5$

Cyano ethyl acetate

Reaction

$2\,Cl - \underset{H}{\overset{H}{C}} - \overset{O}{C} - OH + Na_2CO_3 \longrightarrow 2\,Cl - \underset{H}{\overset{H}{C}} - \overset{O}{C} - ONa + H_2O + CO_2$

monochloro acetic acid

and,

$2\,Cl - \underset{H}{\overset{H}{C}} - \overset{O}{C} - ONa + 2NaCN \longrightarrow 2N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - ONa + 2NaCl$

Na salt of cyano acetic acid

then,

$2N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - ONa + 2HCl \longrightarrow 2N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - OH + 2NaCl$

cyano acetic acid

finally,

$2N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - OH + 2C_2H_5OH \xrightarrow{H_2SO_4} 2N \equiv C - \underset{H}{\overset{H}{C}} - \overset{O}{C} - OC_2H_5 + 2H_2O$

cyano ethyl acetate

2. Reactants

monochloro acetic acid
Sodium cyanide
Ethyl alcohol

3. Reagents

Sodium carbonate
Hydrochloric acid
Sulfuric acid

4. Yield

77%

5. Unit operations

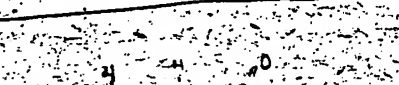
$A_{10} - B_2 - C_9 - D_2 - E_1 - H_3 - J_9 - L_2 - P_{16}$

6. Solvents

Ethyl alcohol (95%)
Benzene

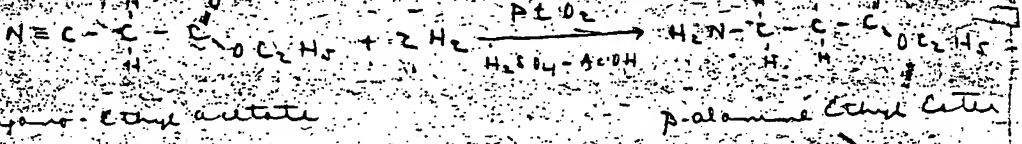
Exp. No. 2

Cyano ethyl acetate



β-alanine ethyl ester

1. Reaction



Cyano ethyl acetate

β-alanine ethyl ester

2. Reactants

Cyano ethyl acetate

Hydrogen

3. Reagents

platinum oxide (catalyst)

sulfuric acid

acetic acid

sodium hydroxide

sodium carbonate

4. Yield

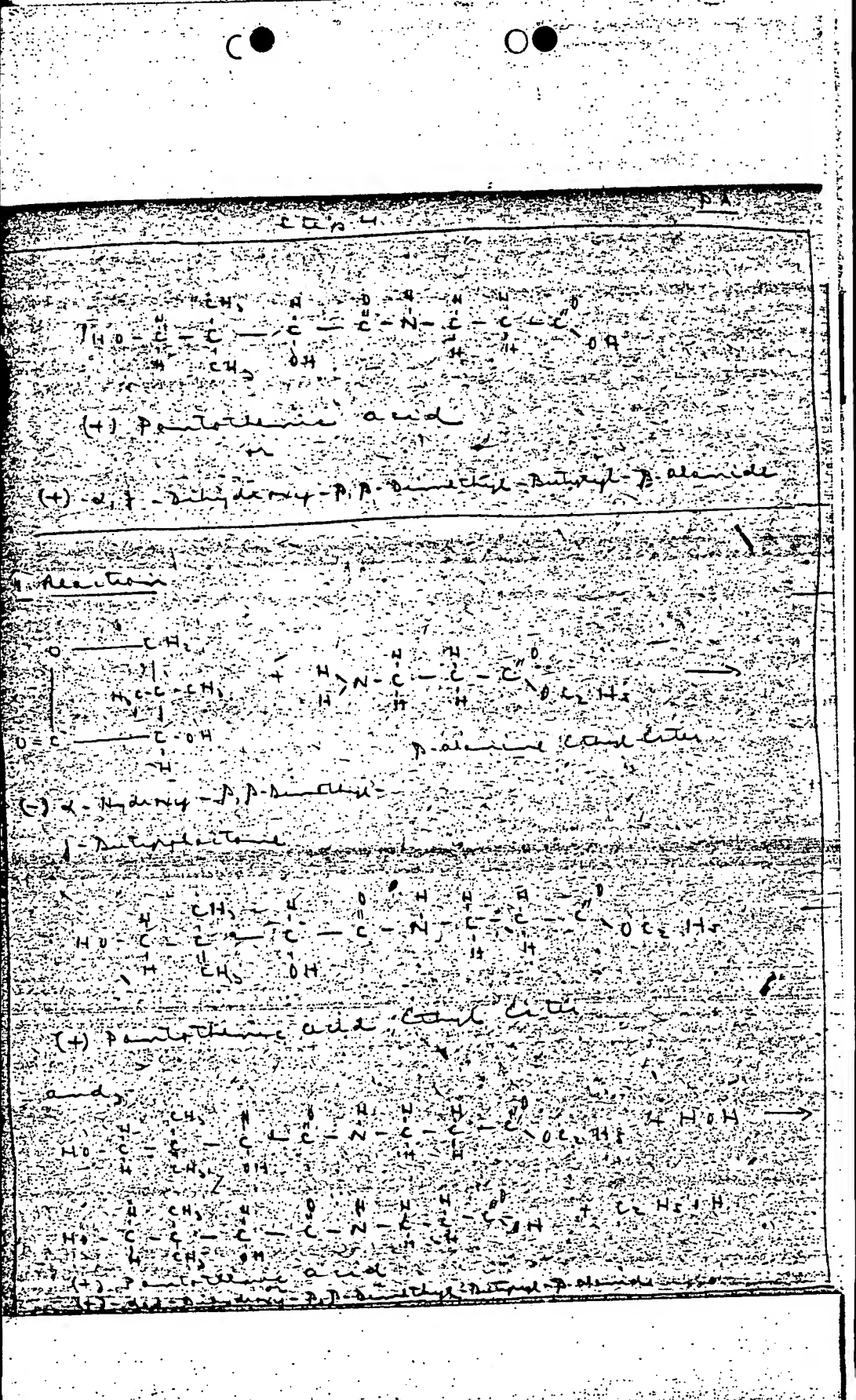
74-76

5. Unit operations

A, B, B1, C, D, D2, E, E1, G, H, J, J6, L, P, O

6. Solvents

Ethyl ether


(+) Pantothenic acid
(+) - α, γ - Dihydroxy - β, β - Dimethyl - Butyryl - β - alanide
Reaction
(-) α - Hydroxy - β, β - Dimethyl -
γ - Butyrolactone
β - alanine Condensation
(+) Pantothenic acid Calcium salt
and

Step 4 (cont'd) F-A

2. Reactants

(-)-α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

β-alanine ethyl ester

Water

3. Reagents

Barium Hydroxide

Sulfuric acid

Pyridine

4. Yield

6.1%

5. Unit operations

A_{22} - D_1 - C_1 - D_4 - E_3 - I_3 - J_{19} - L_6 - N_1 - P_{23}

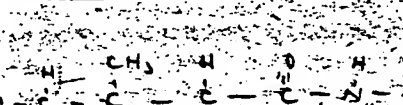
6. Solvents

Methyl alcohol

acetone

ether

Step 5

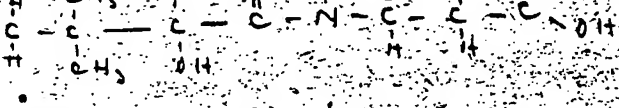


(+) Calcium Pantothenate

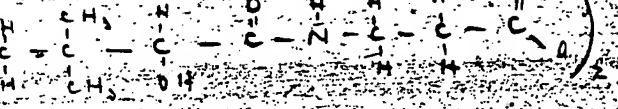
or

Ca salt of (+)-α,γ-Dihydroxy-β,β-Dimethyl-Butyryl-β-Ala

1. Reaction



(+) Pantothenic acid



(+) Calcium Pantothenate

or

Ca salt of (+)-α,γ-Dihydroxy-β,β-Dimethyl-Butyryl-β-alanide

2. Reactants

(+) Pantothenic acid

calcium carbonate

3. Reagents

None

4. Yield

82 %

5. Unit operations

A, B, D, D, I, J, N, P

6. Solvents

Methyl alcohol

Lot 1

A N

B II

C III

D II

E I

H I

I I

J II

L I

N II

P II

Lot 2

A III

B II

C III

D III

E I

H I

I I

J III

L I

N I

P III

Lot 3

A III III II

B III

C III

D III

E I

H II

I II

J III

L III

N II

P III

A 𝍸𝍸𝍸		A 𝍸𝍸	A 𝍸𝍸𝍸𝍸𝍸
B 𝍸		B 𝍸	B 𝍸
C 𝍸𝍸𝍸		C 𝍸	C 𝍸𝍸
D 𝍸		D 𝍸	D 𝍸𝍸𝍸
E 𝍸		E 𝍸	E 𝍸𝍸
H 𝍸𝍸		G 𝍸	H 𝍸𝍸
J 𝍸𝍸𝍸		H 𝍸	J 𝍸𝍸𝍸
L 𝍸		J 𝍸	L 𝍸𝍸
P 𝍸𝍸𝍸𝍸		L 𝍸	N 𝍸
		P 𝍸𝍸	P 𝍸𝍸𝍸𝍸𝍸𝍸

materials used in Part A

material	lbs
Isobutyraldehyde	0.29
Formalin (40% formaldehyde)	0.32
K_2CO_3	2.95
monobasic acetic acid	3.16
Na_2CO_3	1.93
NaCN	7.30
Hg, 3 6 78	4.67
KCN	1.024
$CaCl_2$	0.46
$CaC_2O_4 \cdot 2H_2O$	0.52
NaOH	0.94
Hydrogen	0.11
Quinine hydrochloride	0.16
$Ba(OH)_2 \cdot 8H_2O$	6.57
Pyridine	0.32
$CaCO_3$	0.32

PA → Ca PA

$\frac{439.4}{276.5\ (0.32)} \times 3.20 = 3.59$ # PA ⇌ 1.12 # PA

1.0 = 2.59

3.5

1.0 #$CaCl_2$ ⇌ 0.32 # CaO_2

PA Synthesis

$\frac{439.4}{219.2\ (0.61)} \times 3.59 = 3.49$ # (-) Pantolactone

⇌ 1.09 # (-) Pantolactone

$\frac{7.5}{3.75} = 3.49$ #

6.97 # β-alanine ethyl ester

⇌ 2.18 # β-alanine ethyl ester

$\frac{21.5}{3.75} \times 3.49 \times 1.05 = 20.5$ # $Na(H)_2PO_4 \cdot H_2O$ ⇌ 6.57 #

$\frac{13.2 \times 1.84}{3.75} \times 3.49 \times 0.5 = 6.39$ # H_2SO_4 ⇌ 2.15 #

$\frac{20.5}{3.75} \times 0.05\ (5.71) = 1.03$ # pyridine ⇌ 0

β-alanine EE synthesis

$\frac{43.1}{71.1}\ (0.74) \times 6.97 = 9.09$ # cyano-acetic acetate

⇌ 2.84 # cyano-acetic acetate

$\frac{10.6}{3.0} \times 9.09 \times 1.1 = 0.35$ # H_2 ⇌ 0.11 # H_2

$\frac{8.2}{3.0} \times 9.09 = 0.252$ # NaOH ⇌ 0.79 # NaOH

$\frac{25.0}{3.0} \times 9.09 = 75.8$ # K_2CO_3 ⇌ 23.7 # K_2CO_3

1.77 # H_2SO_4

2,2-Dimethylbutane → (±)-3,3-Dimethylbutan-2-ol

$\frac{120.1}{120.1 + (2 \times 1.01)} \times 2.49 = 2.32$ # 2,2-Dimethylbutane

$\frac{7.13}{2} \times 1.13 = 4.03$ # NaOH ≈ 0.12 # NaOH

$\frac{13.45 \times 1.19}{21} \times 1.13 = 0.86$ # H_2 ≈ 0.27 # H_2

$\frac{9.6 - (2.07 + 1.12)}{2} \times 1.13 = 0.517$ # Raney Ni ≈ 0.16 # Raney Ni

Prop-1-en-2-ol → 1,2-Dibromo-2-methylpropane

$\frac{102.1}{120.1 + (0.79)} \times 1.13 = 1.12$ # 2-Methylprop-1-en-2-ol

≈ 0.35 #

$\frac{98}{102} \times 1.12 = 1.08$ # KCN ≈ 0.34 # KCN

$\frac{133}{102} \times 1.12 = 1.46$ # $CaCl_2$ ≈ 0.46 # $CaCl_2$

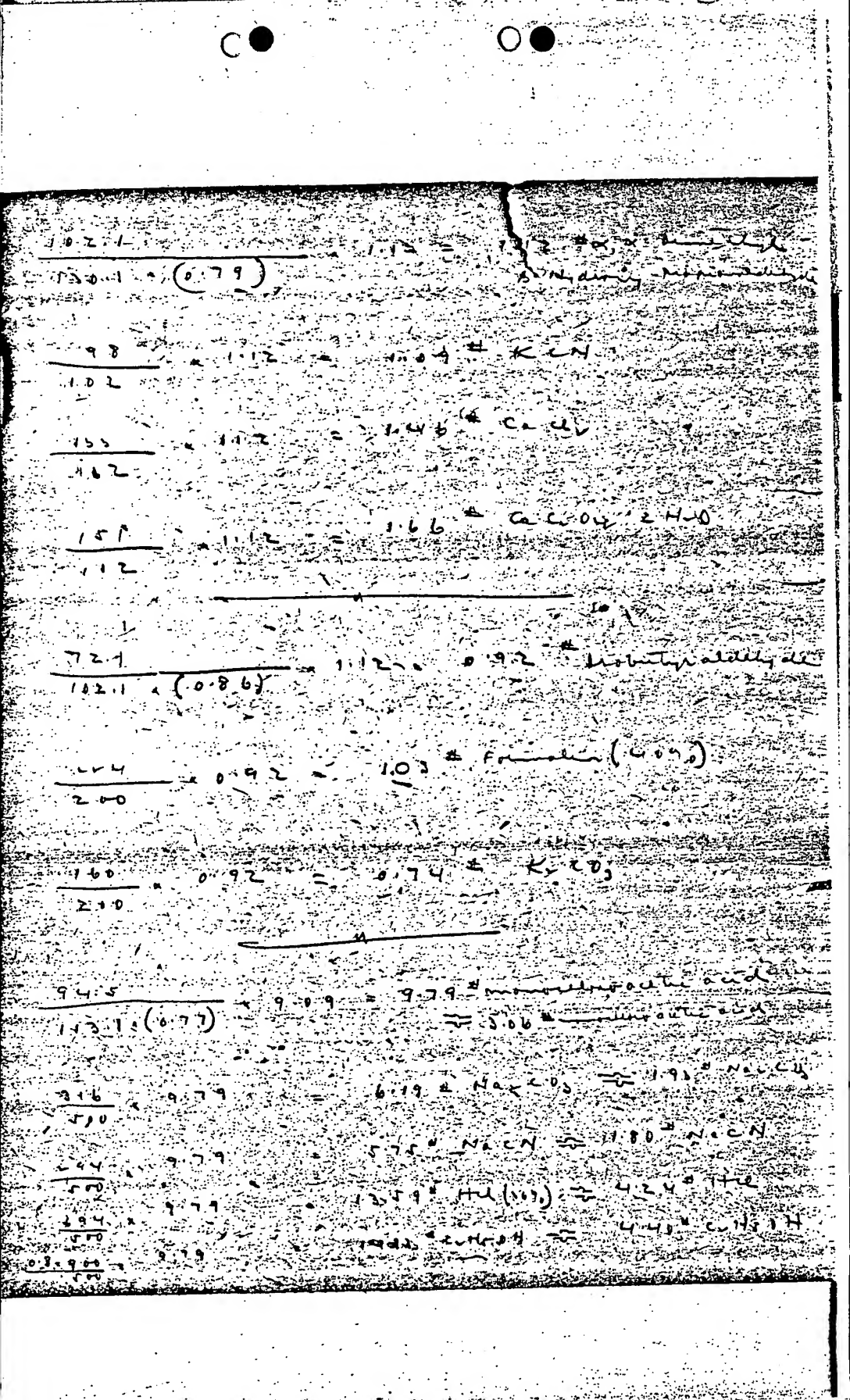
$\frac{151}{102} \times 1.12 = 1.66$ # $CaCl_2 \cdot 4H_2O$ ≈ 0.52 #

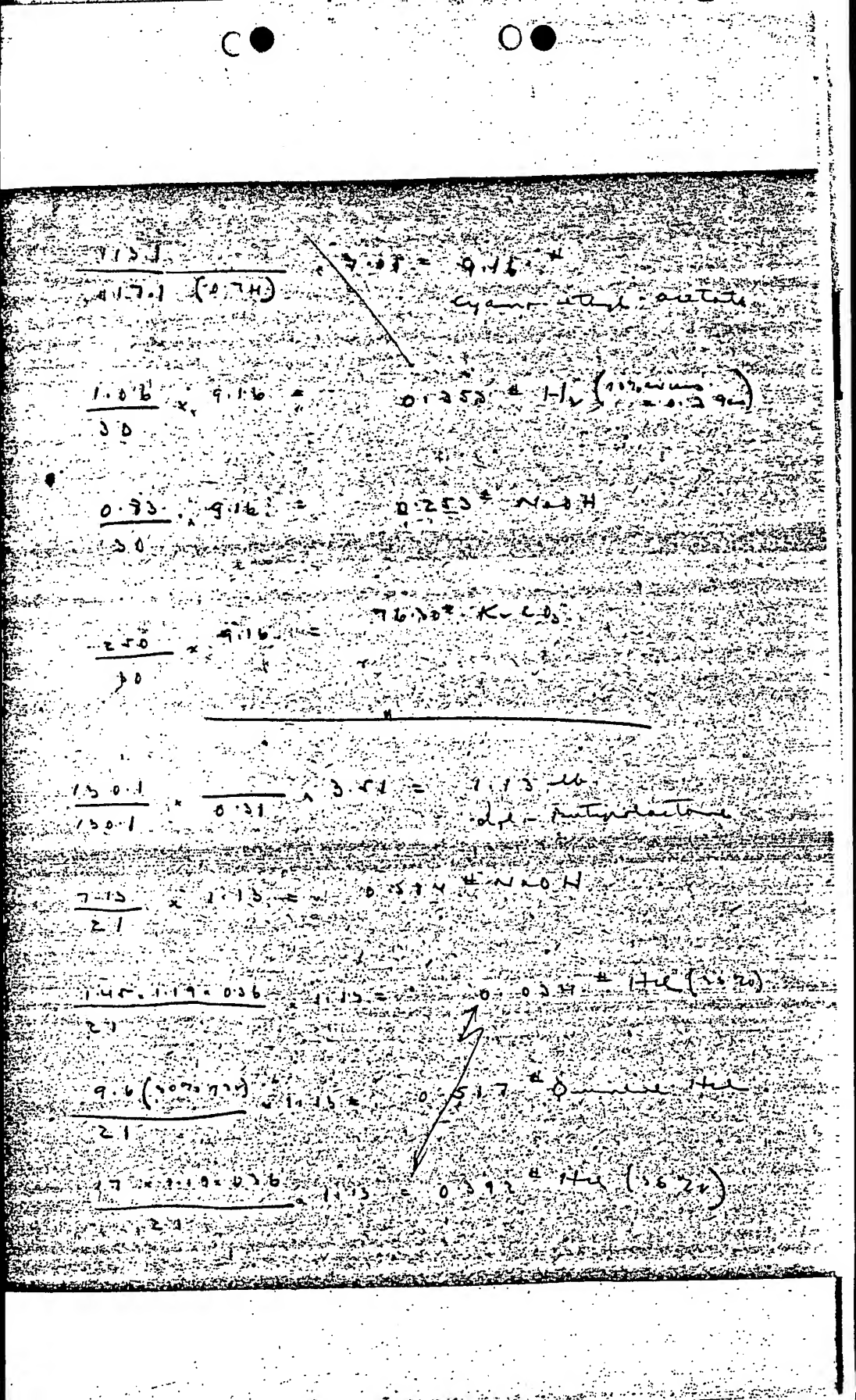
2-Methylprop-1-en-2-ol → 2-Methylpropanal

$\frac{72.1}{112.1\ (0.76)} \times 1.12 = 0.92$ # 2-Methylpropanal ≈ 0.29 # 2-Methylpropanal

$\frac{224}{200} \times 0.92 = 1.03$ # Pyridine (d 0.98) ≈ 0.32 # Pyridine

$\frac{139}{200} \times 0.92 = 0.776$ # $K_2Cr_2O_7$ ≈ 0.23 # $K_2Cr_2O_7$





A Fluid Transfer (Liquid + Gases)

B Fluid Transfer (Conveying)

C Heat Transmission

D Evaporation

E Extraction

F Adsorption

G Gas absorption

H Distillation

J Drying

I Agitation

K Crushing + Grinding

L Filtration

M Classification

N Crystallization

O Sublimation

P Proportioning + Weighing (Liquids + Solids)

Q Air Conditioning (Temp + Humidity + Ventilation)

ORGANIC SYNTHESES

I

α-ALANINE

(α-Aminopropionic Acid)

Submitted by Roy Cloutier and Treat Davies Stair.
Checked by Walter E. Bachmann and W. S. McPhee.

1. Procedure

To a cold (0–5°) solution of 202 g. (3.6 moles) of potassium hydroxide (sticks) in 750 cc. of distilled water is added slowly with stirring 56.65 g. (0.35 mole) of bromine. This solution is chilled to 0° and 32.2 g. (0.5 mole) of succinimide (p. 75) is added with hand stirring. The mixture is warmed in a water bath to 35–40°, then it becomes colorless and is held at that temperature for one hour (Note 1). After being allowed to stand overnight at room temperature, it is acidified to Congo red with concentrated hydrochloric acid (about 300 cc., sp. gr. 1.18) (Note 2) and evaporated to dryness on a steam bath under reduced pressure. The residue is treated with 1 l. of warm 95 per cent alcohol, the undissolved potassium bromide is filtered off and washed with 50–100 cc. of cold alcohol in small portions. The filtrate and washings are combined and evaporated to dryness under reduced pressure, and the residue is extracted with 100 cc. of 95 per cent alcohol. The resulting solution is again evaporated to dryness and the residue finally extracted with 250 cc. of hot absolute alcohol (Note 3). After filtering off the bulk of the alcohol this

extract is diluted with about 100 cc. of distilled water and shaken out twice with 50-cc. portions of ether. The ether extracts are discarded (Note 4).

The aqueous solution is freed of ether and alcohol and then boiled under reflux for one to one and a half hours in order to hydrolyze any chloramine ester. After evaporation under reduced pressure to remove as much as possible of the excess hydrochloric acid, the residue is dissolved in water and diluted to exactly 100 cc. A 5-cc. portion of this solution is withdrawn for determination of total halides. A suspension of silver oxide, prepared from 10 per cent more than the equivalent quantity of silver nitrate (Note 5), is added to the remaining portion of the solution, and the mixture is stirred well in order to bring about complete precipitation of the halides. After standing overnight the precipitate is filtered off and washed with water. The filtrate and washings are concentrated under reduced pressure to about 100 cc., acidified with hydrogen sulfide, and filtered through a thin layer of decolorizing carbon. The colorless filtrate is evaporated to a volume of about 100 cc., treated with decolorizing carbon if necessary, concentrated on the steam bath until crystallization begins, and chilled. The crystals are filtered with suction, washed with a little cold alcohol, and dried. A further crop is obtained by concentrating the mother liquor and again chilling (Note 6). The combined crops (2.5–3.0 g., m.p. 189–192°) are recrystallized from water, employing the same procedure, and yield [illegible] (1.5–2.5 g., 20–30 per cent of the theoretical amount) of pure adrenine, which melts at 197–198° (corr.) with decomposition. About 2 g. less pure product can be secured from the final mother liquors.

Notes

1. The odor of ammonia is perceptible, indicating some hydrolysis.

2. On acidification a small amount of ammonia may be liberated; this is removed rapidly during the subsequent evaporation.

3. If the last extraction the alcohol-insoluble material may be removed advantageously with a centrifuge.

This ether extraction removes small quantities of succinic acid and its esters.

The silver oxide is prepared by dissolving the silver nitrate in about five parts of cold water and adding a slight excess of pure sodium hydroxide in 10 per cent solution. The precipitate is well stirred, collected by filtration or centrifuging, and washed free of sodium salts. It should not be dried before use.

The final mother liquor consists of a rather viscous solution containing uncrystallizable by-products.

Methods of Preparation

The above directions are based upon the methods of Hoogewerff and Van Dorp,[1] as modified by Holm[2] and by Hale and Houtz.[3] Alanine has also been prepared by the action of hypobromite upon succinimide and hydrolysis of the resulting α-aminopropionic acid,[4] by the action of ammonia upon β-iodopropionic acid,[5] by the hydrolysis of methyl carbomethoxy-α-aminopropionate obtained by the action of sodium methoxide on bromosuccinimide,[6] by the reduction of α-nitropropionic acid,[7] by heating ethyl acrylate with alcoholic ammonia,[8] from succinyl glycine ester by the azide synthesis,[9] and by the action of liquid ammonia upon methyl α-bromopropionate.[10]

1. Hoogewerff and Van Dorp, *Rec. trav. chim.* **10**, 5 (1891).
2. Holm, *Ber.* **25**, (1892).
3. Hale and Houtz, *J. Am. Chem. Soc.* **42**, 704 (1920).
4. Weidel and Roithner, *Monatsh.* **7**, 372 (1886).
5. Hantzsch, *Ber.* **25**, (1892). Holde, *Ber.* **37**, 1268 (1904). Hale and Britton, *J. Am. Chem. Soc.* **42**, (1920).
6. Fischer and Scheibler, *Ann. Chem.* **365**, 212, 220 (1909).
7. Erlenmeyer, *Ann.* **264**, 228 (1891).
8. Curtius, *Ber.* **19**, 779 (1886).
9. Curtius and Hedenstroem, *J. prakt. Chem.* **82**, 549 (1910).
10. Fischer, *Ann.* **365**, 208 (1910).

BIOLOGICAL ACTIVITY OF ARSENIC IN ATOPHENIC ACID

ARYLIDOQUINONE OXIDES

Total Synthesis of Pantothenic Acid

By Robert R. Williams and John M. Bobbitt

Received May 10, 1940

Pantothenic Acid, the Total Synthesis of Pure Pantothenic Acid

[illegible] Vol. 62

[illegible] Williams for making available to them much unpublished [illegible] and to Merck & Co. for [illegible] gifts. They further wish to acknowledge their appreciation for the help given by Messrs. R. E. Pratt and R. A. Mitchell during the summer of 1939. They also wish to express their indebtedness to Drs. A. Moffat and K. Folkers for their interest and advice, to Messrs. D. F. Hayman and S. W. [illegible] for carrying out the microanalyses, and to Messrs. [illegible] for the assistance throughout the investigation.

Summary

[illegible] of pantothenic acid have been [illegible] and from the hydrolysis of these compounds a crystalline lactone has been isolated. [illegible] dihydroxy-3,3-dimethylbutyric [illegible] by alternative methods.

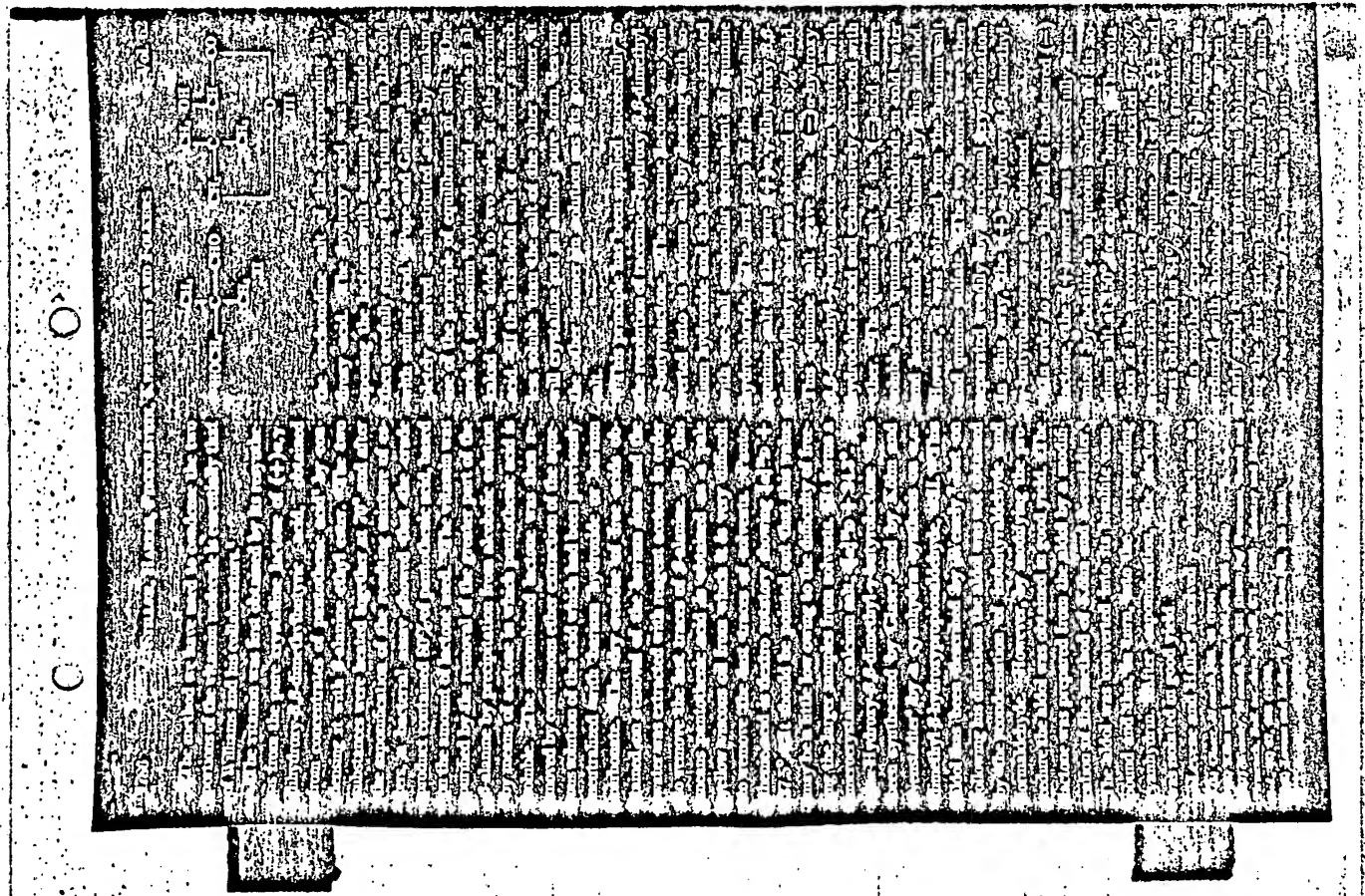
[illegible]

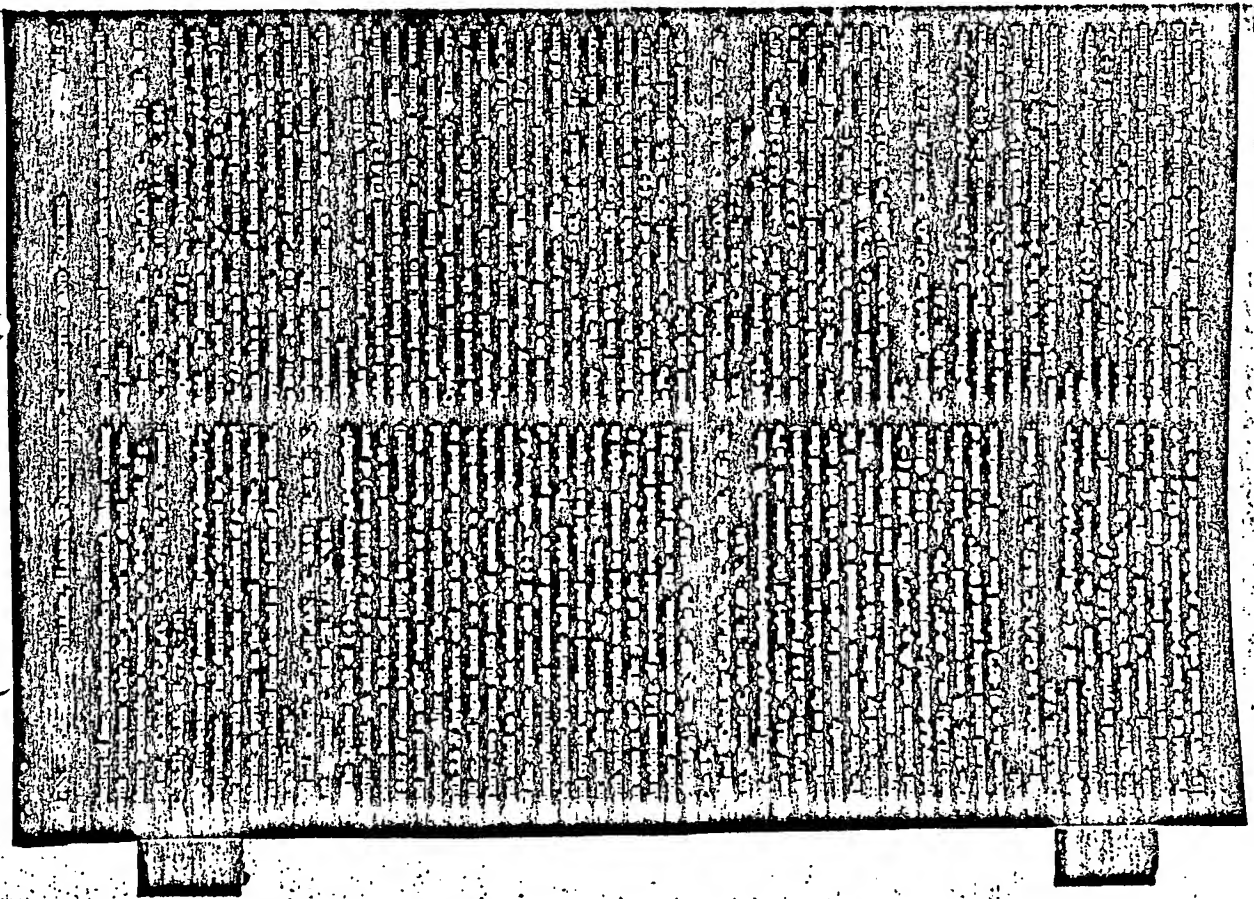
[illegible] May 9, 1940

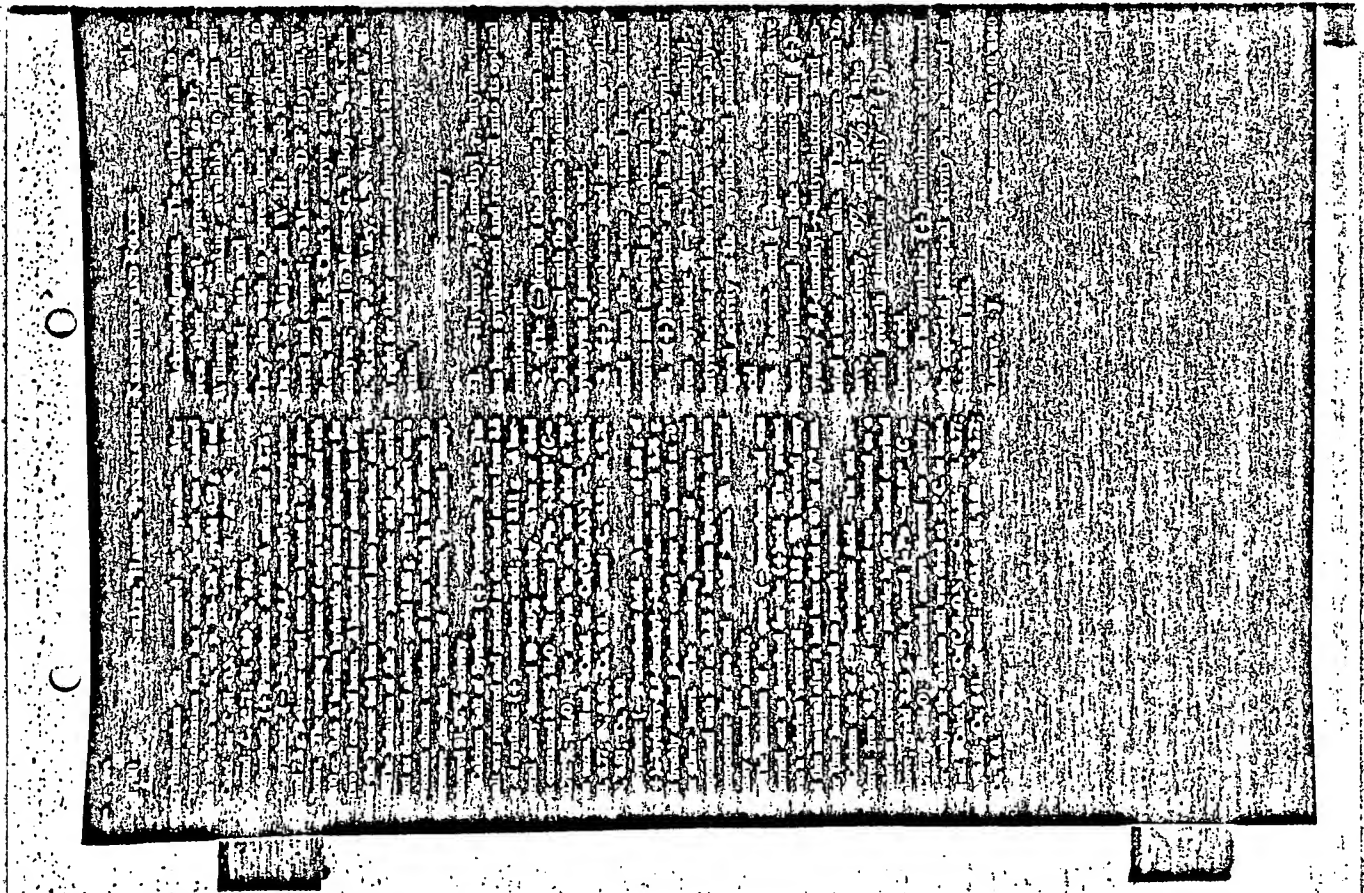
Pantothenic Acid. VII. Partial and Total Synthesis Studies

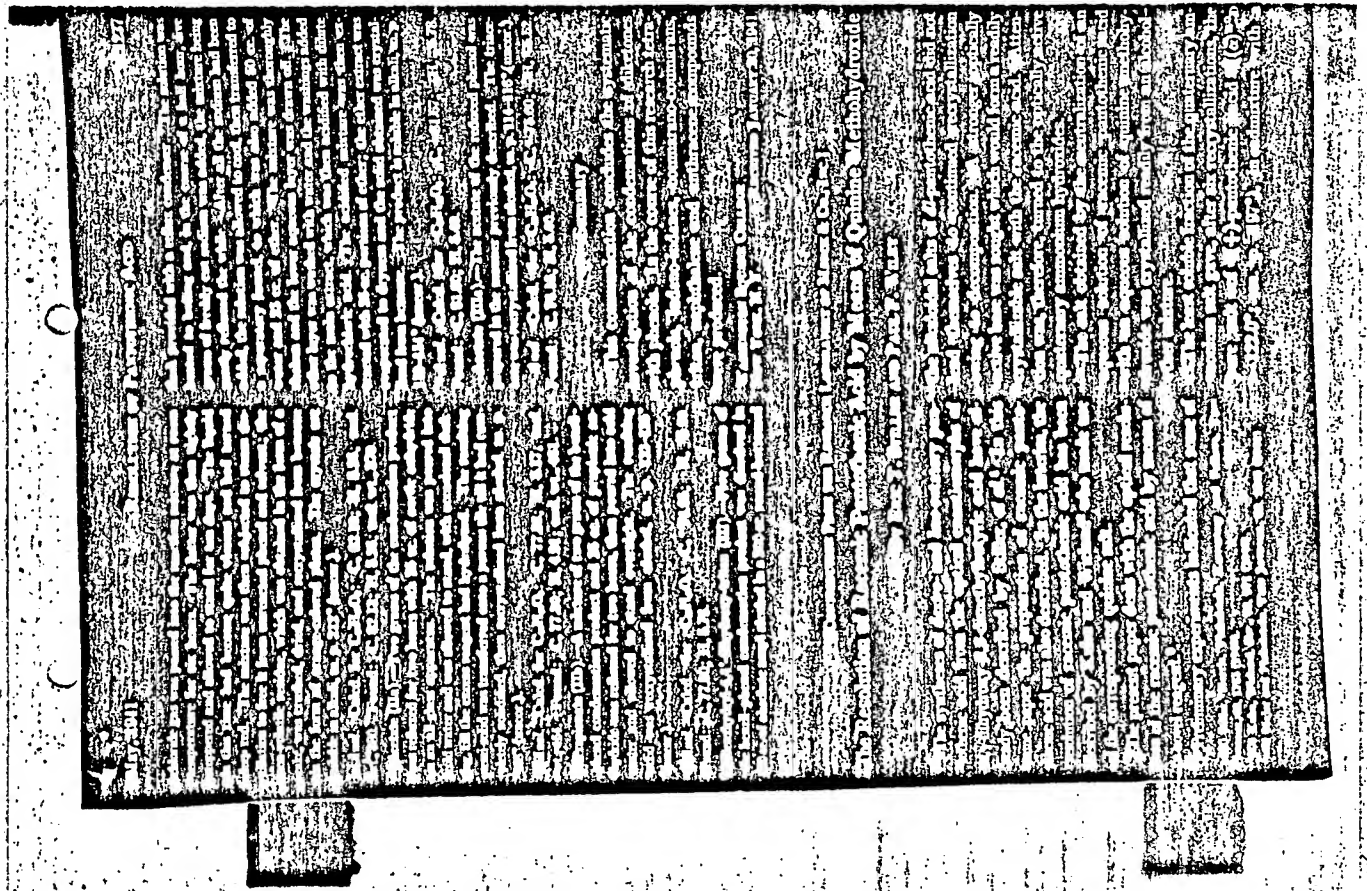
By Robert J. Williams, Charles M. Mason, Harry H. Weinstock, Jr., and Reginald H. Smith

[illegible]









[illegible]

NOTES

advantages over that of Reichstein and Grüssner[2] and over the two step procedure of Kohn and Neustädter[3] as modified by Stiller, *et al.*,[4] it seemed desirable to publish the details.

Experimental

α,α-Dimethyl-β-hydroxypropionaldehyde.—This compound was prepared by the method of Wessely,[5] with the exception that the reaction flask was cooled in an ice-bath during the initial vigorous stage of the reaction.

α-Hydroxy-β,β-dimethyl-γ-butyrolactone.—Crude α,α-dimethyl-β-hydroxypropionaldehyde (102 g., 1 mole) was dissolved in 1 liter of water at 60–70°. The solution was cooled under the tap and a cold solution of 133 g. of calcium chloride and 98 g. of potassium cyanide was added rapidly. The flask was stoppered (to exclude carbon dioxide) and was allowed to stand at room temperature with occasional shaking for eighteen hours. The solution was then heated on the steam cone to 70–80° and 151 g. of oxalic acid dihydrate was added. The calcium oxalate was removed by filtration and the filtrate was concentrated to a gum under reduced pressure. It is essential that as much water as possible be removed at this point. The residue was extracted with 1 liter of dry acetone and the insoluble material was removed by filtration. The filtrate was concentrated to a viscous oil under reduced pressure. The oil was taken up in dry acetone and the solution was filtered. The acetone was removed and the residue was fractionated under reduced pressure. The lactone distilled at 122–130° (18 mm.) as an oil which immediately solidified to a glass in the receiver. The yield of lactone melting at 75–80° was 100–106 g. (77–82% of the theoretical amount). The [illegible] of the [illegible] melted at 137–138° as reported by Stiller, *et al.*[4]

The unusual ease of hydrolysis of the nitrile is interesting in view of the history of the [illegible] group in [illegible] acid.

(2) [illegible]
(3) Stiller, *et al.*, This Journal, **61**, [illegible]
(5) Wessely, *Monatsh.*, **22**, [illegible]

Division of Biochemistry
Noyes Laboratory of Chemistry
Urbana, Illinois Received [illegible], 1940

Note on the Absorption Spectra of Some Alkyl Chrysenes

By [illegible] R. [illegible] Jones

The absorption spectra of [illegible]-methyl-, [illegible]-dimethyl-, [illegible]-dimethyl- and 4,5-methylenechrysene recently have been determined in these laboratories. The wave lengths and intensities of the various maxima are summarized in Table I and the curves are given in Figs. 1, 2. The experimental technique has been described previously.[3] The spectra of [illegible]-methyl and [illegible]-dimethyl-

(1) [illegible]
(2) [illegible]
(3) [illegible]

TABLE I

WAVE LENGTHS (Å.) OF THE MAXIMA AND CORRESPONDING INTENSITIES (LOG E_{max}) OF THE SPECTRA OF SOME ALKYL AND ALKYLENE-CHRYSENE DERIVATIVES (SOLVENT ETHANOL)

	Max.	Intensity
[illegible]-Methylchrysene	2705	.98
	2865	.99
	3005	.98
	3125	.06
	3265	.08
	3505	2.89
	3680	2.90
[illegible]-Dimethylchrysene	2740	.95
	3040	.96
	3225	.08
	3330	.05
	3550	.94
	3745	2.84
[illegible]-Dimethylchrysene	2740	5.10
	2815	5.05
	3120	.15
	3300	.24
	3450	.24
	3800	.87
[illegible]-Methylenechrysene	(2590)	.83
	2655	.99
	2690	.04
	3010	.09
	3180	.07
	3285	.09
	3420	.98
	3465	.82
	3525	.65
	3606	.89

chrysene resemble that of the unsubstituted hydrocarbon apart from the usual shift to longer wave lengths and some loss of fine structure. 4,5-Dimethylchrysene differs somewhat from the other two methyl derivatives, the most intense maximum showing some resolution while at longer wave lengths the intensity of absorption is greater and the resolution less.

The spectrum of 4,5-methylenechrysene (I) is particularly interesting as in the 1,2-benzanthracene series such a bridge methylene group has been observed to produce a considerable change in the spectrum including an increase in the amount of fine structure resolved.[2] The spectrum of 4,5-methylenechrysene also shows an increase in the amount of fine structure, particularly if comparison is made with 4,5-dimethylchrysene, substituted at the same position (Fig. 2). A corresponding comparison between the dimethyl and the methylene derivative is not possible in the

(2) [illegible]
(3) Jones, This Journal, **63**, 151 (1941).

Patented Mar. 11, 1941

2,234,680

UNITED STATES PATENT OFFICE

2,234,680

PROCESS OF PREPARING PANTOTHENIC ACID

Marjorie B. Moore, Waukegan, Ill., assignor to Abbott Laboratories, North Chicago, Ill., a corporation of Illinois

No Drawing. Application July 22, 1940, Serial No. 346,897

2 Claims. (Cl. 260—534)

The present invention relates to the process of preparing a complex organic acid known in the art as pantothenic acid.

Pantothenic acid, a member of the class of "B" vitamins may be represented by the following formula:

$$HOCH_2C(CH_3)_2—CHOH—CONHCH_2CH_2COOH$$

and its synthesis due to its complex structure has presented many difficulties. The presence of various type reactive groups in the molecule, for example, makes the use of acid chlorides extremely difficult and as a result the synthesis of the acid particularly in a satisfactory form for use in the therapeutic field has presented the art with the problem of process of preparation.

The principal object of the present invention is to provide the art with a satisfactory process for the preparation of pantothenic acid resulting in the synthesis of the acid in the desired form for therapeutic use.

Other objects of the present invention will be apparent as the description proceeds.

I have discovered after an extensive research investigation that pantothenic acid may be prepared in the desired form by heating i. e. fusing, B-alanine (B-amino-propionic acid) with a member selected from the group consisting of α,γ-dihydroxy-B,B-dimethyl-n-butyric acid and α-hydroxy-B,B-dimethyl-butyro-γ-lactone. This method (employing the specified butyric acid or related lactone) has demonstrated that it is free from the objections found in other processes and to result in a yield of final product excellently suited for use in the therapeutic field. The following example will serve for illustrative purposes:

Example

About 130 grams (1 mole) of α-hydroxy-B,B-dimethyl-butyro-γ-lactone and about 89 grams (1 mole) of B-alanine are mixed and gradually heated with occasional stirring. Up to about 178° C. crystals of B-alanine are present and there is no sign of chemical reaction. Around this temperature (i. e. 178° C.), however, the mixture begins to bubble vigorously indicating that a chemical reaction is under way.

The temperature of the reaction mixture is ordinarily maintained at, or preferably above 178° C. for about 15 minutes or longer to complete the reaction indicated by no further bubbling. The final liquid reaction product which is almost colorless and does not deposit crystals i. e. remains substantially free from solid material when cooled, may be used directly in the form obtained as further treatment or purification is unnecessary. If desired the final acid product may be reacted to form salts e. g. calcium pantothenate, and be administered in such form.

It will be understood that the present invention is not limited to the above illustrative example. All modifications of the present invention are intended to be covered by the following claims.

I claim:

1. The process of preparing pantothenic acid of the vitamin B complex which comprises fusing a mixture made up of B-alanine and a member selected from the group consisting of α,γ-dihydroxy-B,B-dimethyl-n-butyric acid and α-hydroxy-B,B-dimethyl-butyro-γ-lactone.

2. The process of preparing pantothenic acid of the vitamin B complex which comprises heating a mixture made up of about molecular proportions of α-hydroxy-B,B-dimethyl-butyro-γ-lactone and B-amino-propionic acid to a temperature of above 178° C. until complete fusion occurs and the resulting liquid reaction product remains substantially free from solid material on standing.

MARJORIE B. MOORE.

erhalten. Nach 2 Tagen destilliert man bis auf 10 cm³ ab und saugt die beim Erkalten ausgeschiedenen Krystalle ab; Ausbeute 3,4 g. Die Mutterlauge wird nach Zusatz von 30 cm³ Eisessig auf dem Wasserbad auf die Hälfte eingedampft und gibt beim Erkalten 4,6 g braungelbe Krystalle, die nach Umlösen aus der 25-fachen Menge Alkohol bei 125—126° schmelzen. Die erstgenannte Krystallisation (3,4 g) erweist sich nach Umkrystallisieren als identisch, enthält aber kleine Mengen höherschmelzender Anteile. Gut löslich in Chloroform und warmem Eisessig, weniger in Alkohol.

3,349 mg Subst. gaben 6,090 mg CO_2 und 0,965 mg H_2O

$C_{14}H_{10}O_4N_2Cl_2$ Ber. C 49,27 H 2,93%

Gef. „ 49,59 „ 3,22%

Eine 30 Minuten dauernde Chlorierung von 2 g eines Gemisches von cis- und trans-o,p'-Dinitro-stilben ergab 0,7 g Dichlorid vom Smp. 204°.

3,990 mg Subst. gaben 7,240 mg CO_2 und 1,165 mg H_2O

$C_{14}H_{10}O_4N_2Cl_2$ Ber. C 49,27 H 2,93%

Gef. „ 49,50 „ 3,27%

Eine 30 Minuten dauernde Chlorierung von 0,5 g cis-Form ergab umkrystallisiert 0,2 g Dichlorid vom Smp. 204°; Ausbeute 32% der Theorie.

Universität Basel, Anstalt für Organische Chemie.

21. Krystallisiertes Natriumsalz der Pantothensäure

von M. Gätzi-Fichter, H. Reich und T. Reichstein.

(8. II. 41.)

Die von *R. J. Williams* und Mitarbeitern entdeckte Pantothensäure[1]) besitzt erhebliche biologische Bedeutung. Sie wird von vielen Einzellern sowie von höheren Tieren benötigt, und es ist sehr wahrscheinlich, dass sie auch für den Menschen die Rolle eines Vitamins spielt. Sowohl für tierexperimentelle wie für klinische Versuche wäre es daher zweckmässig, einen brauchbaren Standard mit genau bekanntem Gehalt an Pantothensäure zu besitzen. Die freie Säure ist für diesen Zweck wenig geeignet, da sie flüssig ist und nicht krystallisiert, weshalb man keine sicheren Kriterien für ihre Reinheit besitzt. Von Salzen sind bisher lediglich das Chininsalz[2])[3]) sowie das Benzyl-chinuroniumsalz[4]) in krystallisierter Form beschrieben worden. Beide sind für biologische Versuche wenig geeignet. Auf der Suche nach

[1]) Bez. Literatur vgl. das kürzlich erschienene Sammelreferat von *R. J. Williams*, Angew. Ch. 54, 31[illegible] (1941).

[2]) *R. Kuhn, Th. Wieland*, B. 73, 971 (1940); vgl. ferner die Berichtigung, B. 73, 1134 (1940).

[3]) *M. Grüssner, M. Gätzi-Fichter, T. Reichstein*, Helv. 23, 1276 (1940).

[4]) *E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, K. Folkers*, Am. Soc. 62, 1785 (1940). Diese Forscher beschreiben zwar nur das Benzyl-chinuroniumsalz der racemischen Säure. Wie wir fanden, krystallisiert jedoch auch das entsprechende Salz der optisch aktiven l-Form sehr gut. Es bildet aus Aceton (durch Einengen) farblose Drusen vom Smp. 145—146°.

einem krystallisierten Derivat, das auch für klinische Anwendung am Menschen verwendbar ist, fanden wir im Natriumsalz den bisher aus[illegible] geeignetsten Vertreter. Dieses Salz lässt sich leicht bereiten und krystallisiert aus Alkohol unter Zusatz von Aceton oder Äther in gut ausgebildeten, farblosen Nädelchen, die bei 221—222° unzersetzt schmelzen und eine spez. Drehung von [α]D = +29° ± 1° (Wasser enthalten. Das Natriumsalz hat auch den Vorteil, für Injektionszwecke besonders brauchbar zu sein, da Natrium bekanntlich von allen Ionen bei dieser Anwendungsart am besten verträglich ist. Der grösste Nachteil dieses Salzes ist der, dass es sehr hygroskopisch ist und an feuchter Luft bereits nach wenigen Minuten zerfliesst. Es muss somit entweder im Exsikkator oder in luftdicht verschlossenen, am besten zugeschmolzenen Ampullen aufbewahrt werden. Trotzdem scheint es uns, aus den eingangs genannten Gründen, als Standardsubstanz, in biologische Versuche gegenüber allen anderen bisher bekannten Derivaten der Pantothensäure den grössten Vorzug zu besitzen.

Das Natriumsalz wurde zunächst von destilliertem Analysen[illegible] einem (+)-Pantothensäure-äthylester-[illegible] bereitet, aber durch vorsichtige Verseifung mit der berechneten Menge Bariumhydroxyd in das Bariumsalz übergeführt, wurde. Das Bariumsalz wurde dann mit Natriumsulfat umgesetzt. Das Natriumsalz ist ausserdem in einfacherer [illegible] direkt durch Erwärmen von (+)-Oxy-β,β-dimethyl-butyrolacton mit trockenem β-Alanin-natrium erhältlich[illegible]. Am besten arbeitet man diese Reaktion so aus, dass man β-Alanin in der äquimolaren Menge einer trockenen Natriummethylatlösung auf[illegible] Lacton einwirken [illegible]. Nach [illegible] gelegentlichem Stehen bei Zimmertemperatur ist die Umsetzung beendet, und es werden Ausbeuten von [illegible] 90% der Theorie an [illegible] destilliertem Natriumsalz erhalten.

[illegible]

[illegible] Teil.

(+)-Pantothensäure-Natrium.

[illegible] (+)-Pantothensäure-Barium (aus destilliertem Äthylester gewonnen) wurden in ca. 25 cm³ Wasser gelöst und bei 60° möglichst genau mit einer wässrigen Natriumsulfatlösung von derselben Temperatur genau ausgefällt. Hierzu wurden etwa 0,57 g wasserfreies Natriumsulfat benötigt. Dann wurde sofort abgekühlt, das Bariumsulfat durch Zentrifugieren entfernt und die klare Lösung im Vakuum

[illegible]

[illegible]

[illegible]

eingedampft. Der verbleibende Sirup krystallisierte nach mehrtägigem Stehen im Vakuum-Exsikkator über Calciumchlorid. Nach Entnahme von etwas Impfmaterial wurde in wenig absolutem Alkohol gelöst und die leicht trübe Lösung über einer Spur Kohle blank filtriert und unter Umschwenken mit Aceton bis knapp zum Auftreten einer bleibenden Trübung versetzt, die durch Zusatz von einem Tropfen Alkohol wieder entfernt wurde. Beim Animpfen trat bald reichliche Krystallisation ein, die durch vorsichtigen Acetonzusatz allmählich vervollständigt wurde. Die Krystalle wurden abgenutscht, mit Alkohol-Aceton (1:1), dann (1:2), anschliessend mit reinem Aceton und zuletzt mit Äther gewaschen und im Vakuum über Calciumchlorid getrocknet. Sie schmolzen bei 120—122°. Nochmaliges Umkrystallisieren aus Alkohol-Aceton gab farblose, verfilzte Nadeln, die bei 121—122° korr. unzersetzt schmolzen. Die spez. Drehung betrug: [α]$_D^{20}$ = +29,5° ± 1° (c = 1,9 in Wasser).

[illegible] mg Substanz [illegible] Stunden bei 0,03 mm und Zimmertemperatur getrocknet) [illegible] mg CO$_2$, [illegible] mg H$_2$O.

[illegible] mg Substanz [illegible] cm³ (n = [illegible], p = 0,86 Atm., t = [illegible]°).

Zur Analyse wurde 1 Stunde bei 0,03 mm und 60° getrocknet.

C$_{10}$H$_{19}$O$_5$NCa (273,32) Ber. C 44,81 H 7,09 N 5,13 Ca 14,69%
Gef. „ 44,24 „ 7,01 „ 5,12 „ 14,67%

Das zweimal umkrystallisierte Präparat war merklich weniger hygroskopisch als das nur einmal umkrystallisierte. An feuchter Luft verfliesst es jedoch auch sehr bald.

Ein identisches Produkt wurde in einer Ausbeute von 89% der Theorie auf folgendem Ansatz erhalten: 1,76 g trockenes β-Alanin wurden unter leichtem Wärmen in 30 cm³ einer trockenen Natriummethylat-Lösung gelöst. Die 0,46 g Natrium enthielt. Nach dem Erkalten wurden 2,6 g d(—)-α-Oxy-β,β-dimethyl-butyrolacton zugegeben und die Mischung zwei Tage bei Zimmertemperatur stehen gelassen. Nach dem Eindampfen im Vakuum wurde der gut getrocknete Rückstand aus Alkohol-Aceton wie oben umkrystallisiert.

d(—)-Pantothensaures Natrium.

Das Natriumsalz der d(—)-Pantothensäure wurde in kleiner Menge genau wie oben aus dem Bariumsalz bereitet. Es schmolz nach nur einmaligem Umkrystallisieren bei 120—122° und zeigte eine spez. Drehung von: [α]$_D^{20}$ = +[illegible]° ± 1° (c = 0,875 in Wasser).

[illegible] mg Substanz [illegible] Stunden im Hochvakuum [illegible] (Zimmertemperatur, [illegible]) [illegible] mg CO$_2$, [illegible] mg H$_2$O.

[illegible] mg Substanz [illegible] cm³ (n = [illegible], p = 0,91 Atm., t = [illegible]°).

[illegible] wurden im exsikkatorgetrockneten Präparat der Firma [illegible] [illegible] Feuchtigkeit gefunden.

45. Krystallisierte Chininsalze der [ ] und (+)-Pantothensäure und die biologische Wirksamkeit des [ ]-Pantothensäure-äthylesters

[illegible] (12. IX. 40.)

Vor kurzem beschrieben wir ein einfaches Verfahren zur Herstellung der [ ]-Alaninde von Oxysäuren[1]), welches darauf beruht, dass man Oxylactone mit Estern, Salzen oder Amiden des [ ]-Alanins umsetzt und das insbesondere auch zur Herstellung von Pantothensäure sehr geeignet ist. In verschiedenen, vor kurzem erschienenen Mitteilungen von *Baborovský* und *Walter*[2]), *Williams* und Mitarbeitern[3]), *Stiller* und Mitarbeitern[4]) ist zur Synthese der Pantothensäure und verwandter Stoffe dasselbe Verfahren als besonders geeignet befunden worden. Auch der dort[4]) zur Gewinnung der optisch aktiven Formen beschrittene Weg ist mit dem von uns benutzten fast bis in alle Einzelheiten identisch, so wurde die Spaltung der [ ]-Dioxy-[ ]-dimethylbuttersäure (I) in die optischen Antipoden auch über die Chininsalze versucht. Dies ist kein Zufall, denn von allen leicht zugänglichen Alkaloiden ist für diesen Zweck nur Chinin [illegible]

In unserer letzten Mitteilung wurde nur die Bereitung des [ ]-Pantothensäure-esters beschrieben, wobei einschränkend erwähnt wurde, dass noch weitere Versuche zeigen sollen, ob bei der Bereitung keine partielle Racemisierung eingetreten ist. Es zeigte sich, dass es sich wirklich um die optisch reine Form gehandelt hat. Inzwischen wurde auch der biologisch unwirksame (+)-Pantothensäure-ester bereitet. Da dieser aber gegenüber den von den Amerikanern[5]) beschriebenen wurde, so sollen nur diejenigen Punkte erwähnt werden, die eine Ergänzung darstellen.

Während das zur Bereitung der (+)-Säure als Ausgangsmaterial benötigte [ ]-Lacton (I) mit dem käuflichen Chininsalz sofort in optisch reiner Form erhalten wird, ist das aus dem leichtlöslichen Chininsalz erhältliche [ ]-Lacton (II) [illegible] immer mit etwas Racemat verunreinigt. *Stiller* und Mitarbeiter[4]) gewannen es

[illegible]

[illegible] Helv. 23, 850 (1940).

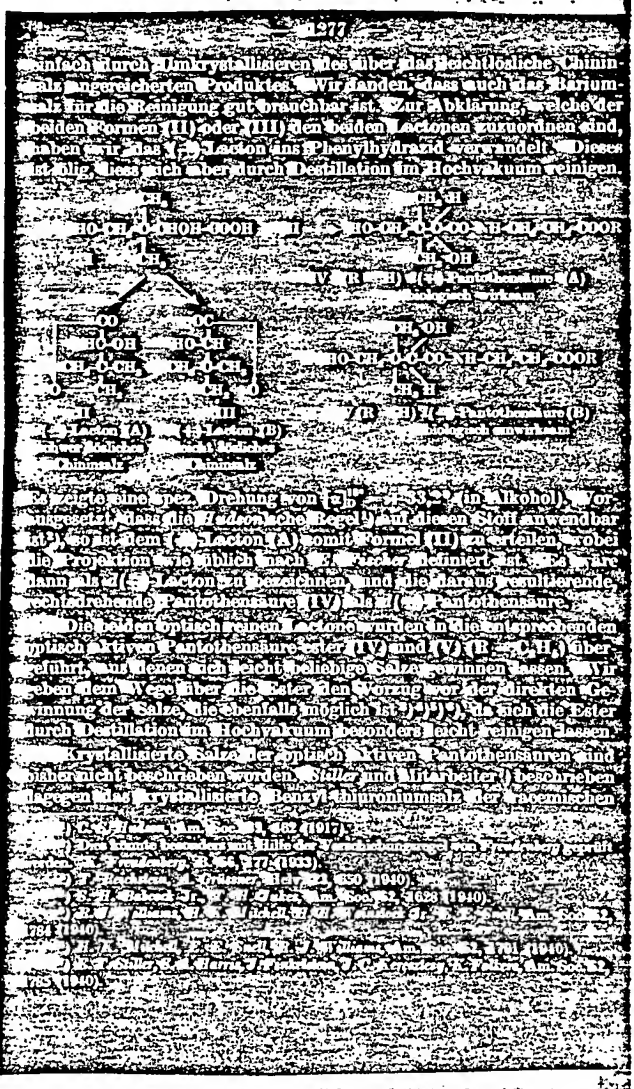
[illegible] 23, 852, 862 (1940).

[illegible] 778 (1940).

[illegible] 23, 1718 (1940).

[illegible] 785 (1940).

einfach durch Umkrystallisieren des über das leichtlösliche Chinin-salz angereicherten Produktes. Wir fanden, daß auch das Benzylamin-salz für die Reinigung gut brauchbar ist. Zur Abklärung, welche der beiden Formen (II) oder (III) den beiden Lactonen zuzuordnen sind, haben wir das (+)-Lacton ins Phenylhydrazid verwandelt. Dieses ist völlig, dessen Ester durch Destillation im Hochvakuum reinigen.



Es zeigte eine spez. Drehung von [α]D = -38° (in Alkohol). Vorausgesetzt, daß die Drehung dieser Base(II) an diesem Stoff ein Maximum ist, so ist dem (+)-Lacton (A) somit Formel (II) zuzuteilen, wobei die Projektion sie üblich nach Fischer definiert ist. Es wäre dann das (+)-Lacton zu bezeichnen, und die daraus resultierende Dihydroxybernsteinsäure (IV) als (+)-Pantothensäure.

Die beiden optisch reinen Lactone wurden in die entsprechenden optisch aktiven Pantothensäure-ester (IV) und (V) (R = C_2H_5) überführt, aus denen sich leicht beliebige Salze gewinnen lassen. Wir geben dem Weg über die Ester den Vorzug vor der direkten Gewinnung der Salze, die ebenfalls möglich ist, da sich die Ester durch Destillation im Hochvakuum besonders leicht reinigen lassen. Krystallisierte Salze der optisch aktiven Pantothensäuren sind bisher nicht beschrieben worden. Stolz und Mitarbeiter[1] beschreiben lediglich das krystallisierte Benzylaminsalz der racemischen

[1] (1917)
(1940)
(1940)
(1940)
(1940)

Pantothensäure, Barium- und Calciumsalze, die sich durch Umfällung reinigen lassen, und zwar nach Angaben der genannten Autoren mikrokrystallin (anisotrop), bieten jedoch keine Gewähr für Reinheit, da sie sich nicht in deutlich ausgebildeten Krystallen erhalten lassen. Auf der Suche nach eindeutig krystallisierbaren Salzen fanden wir im Chinin wieder eine geeignete Base. Mit beiden optisch aktiven Pantothensäuren werden krystallisierte Salze erhalten, die sich in ihrer Löslichkeit, besonders in Aceton sehr stark unterscheiden, so dass auch racemische Pantothensäure mit Hilfe von Chinin in die optisch aktiven Formen gespalten werden kann. Das Chininsalz der biologisch wirksamen (+)-Pantothensäure (IV) ($[\alpha]_D^{20} = +34$) ist in Aceton platzraubend löslich und krystallisiert aus heissem Aceton in farblosen Nädelchen vom Smp. 36° korr., die 1 Mol Wasser enthalten, das sich schwer ganz entfernen lässt. Sie besitzt die spezifische Drehung: $[\alpha]_D^{20} = -95°$ (in Wasser). Das Chininsalz der biologisch unwirksamen (−)-Pantothensäure ist auch in heissem Aceton sehr schwer löslich. Es krystallisiert aus Alkohol in äusserst feinen, nitzigen Nädelchen, die bei 183,5° schmelzen und zeigt die spez. Drehung von $[\alpha]_D^{20} = +21°$ (in Wasser).

Auch die Natriumsalze der beiden optisch aktiven Pantothensäuren sind in reinem krystallinisch erhalten worden, doch handelt es sich um äusserst hygroskopische Substanzen, so dass noch keine [illegible] bestimmungen gemacht werden konnten.

Bezüglich der biologischen Prüfung standen uns bereits ausgedehnte Resultate über die Wirkung der zwei optisch aktiven Pantothensäure-äthylester vor, über die wir folgende Daten aus dem [illegible] biologischen Laboratorium der *F. Hoffmann-La Roche & Co. A.G.*, Basel, orientiert.

Der (+)-Pantothensäure-ester ($C_{11}H_{21}O_5N$) wirkt sich in Dosen von 0,2 mg pro Tag an der Ratte als stark wirksam. Die Gewichtszunahme betrug im Durchschnitt 1,5 g pro Tag, während die Kontrolltiere 0,3 g pro Tag zunahmen. Mit 0,1 mg (+)-Pantothensäure-ester pro Tag war der tägliche Gewichtszuwachs noch etwas grösser, er betrug 1,9 g. Auch bei Zufuhr sehr viel kleinerer Mengen (+)-Pantothensäure-ester, nämlich 1,5 mg, konnte eine [illegible] Gewichtszunahme erzielt werden. Mit 300 γ racemischem Pantothensäure-methylester wurde eine Gewichtszunahme von 1,3 g, mit 600 γ eine solche von 2 g pro Tag erreicht. Die Kontrolltiere nahmen bei diesem Versuch etwas stärker zu, nämlich um 0,5 g täglich, also [illegible] Gewichtsdifferenz zwischen den mit racemischem Pantothensäure-ester gefütterten Tieren und den Kontrollen ist also [illegible] Versuchen mit (+)-Pantothensäure-ester.

[illegible]

Der tägliche Bedarf der Ratte an d(+)-Pantothensäure dürfte bei etwa 10 γ liegen.

Im Gegensatz zum d(+)-Pantothensäure-ester erwies sich der l(−)-Ester in Dosen von 10 γ als ganz unwirksam (s. Kurvenbild S. 280), in solchen von 50 γ als kaum wirksam. Dies bestätigt die Resultate der amerikanischen Forscher [1] [2] [3] und ergänzt sie insofern, als sich an Ratten nicht nur die freie d(+)-Säure und ihre Salze, sondern auch die Ester als wirksam erweisen.

Das racemische Lacton (II) bewirkte an Ratten, die gleichzeitig β-Alanin erhielten, in Dosen von 3 mg pro Tag eine Gewichtszunahme von durchschnittlich 1,2 g täglich, während die Kontrolltiere eine solche von 0,12 g aufwiesen. In einer anderen Versuchsreihe wurde durch tägliche Zulage von 0,5 mg d(−)-Lacton ein Gewichtsanstieg von 1,8 g pro Tag erzielt.

Bemerkenswert ist, dass ausser der Gewichtszunahme auch eine deutliche Vermehrung der Reticulocytenzahlen in den ersten Tagen nach der Pantothensäure-Zufuhr beobachtet wurde. Zur Feststellung, ob es sich dabei um eine spezifische Wirkung der Pantothensäure handelt, sind noch weitere Versuche notwendig. Es wurde auch bei Zufuhr anderer Vitamine eine Zunahme der Reticulocyten festgestellt. So haben *Ferranini* und *Muratori* [4] nach Zufuhr von 5 mg Nicotinsäure an 100 g schweren Ratten erhöhte Reticulocytenzahlen gefunden. *v. Euler* und *Malmberg* [5] haben nach Verabreichung von Ascorbinsäure die gleiche Beobachtung gemacht.

Von Bedeutung wären klinische Versuche darüber, ob sich gewisse Anämien mit Pantothensäure günstig beeinflussen lassen.

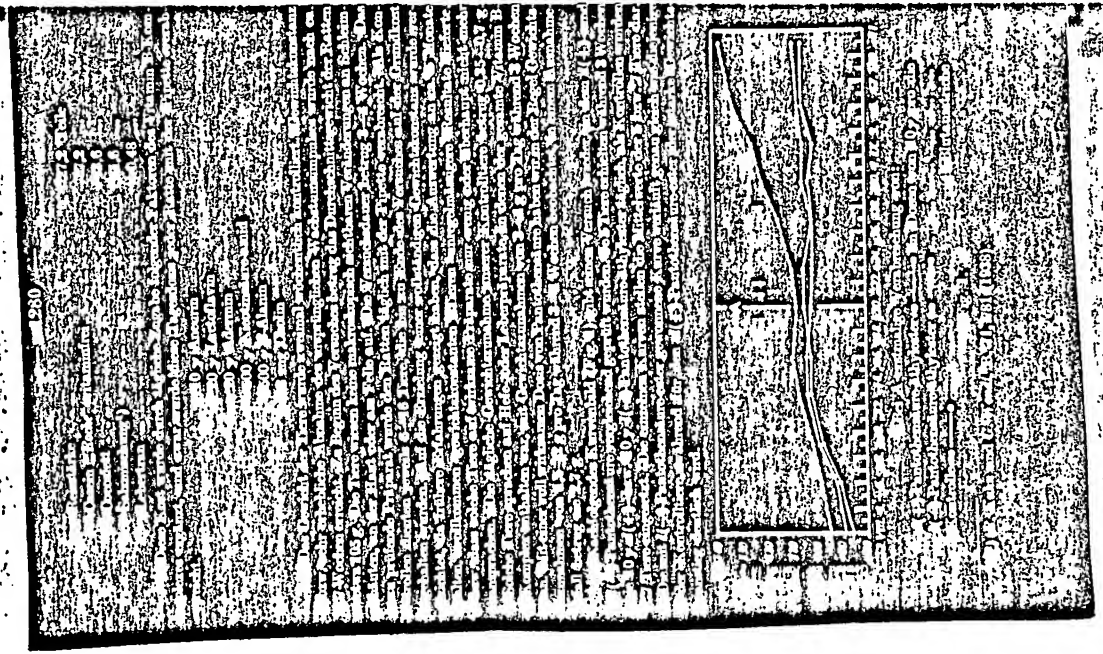
Biologische Prüfung der Pantothensäure

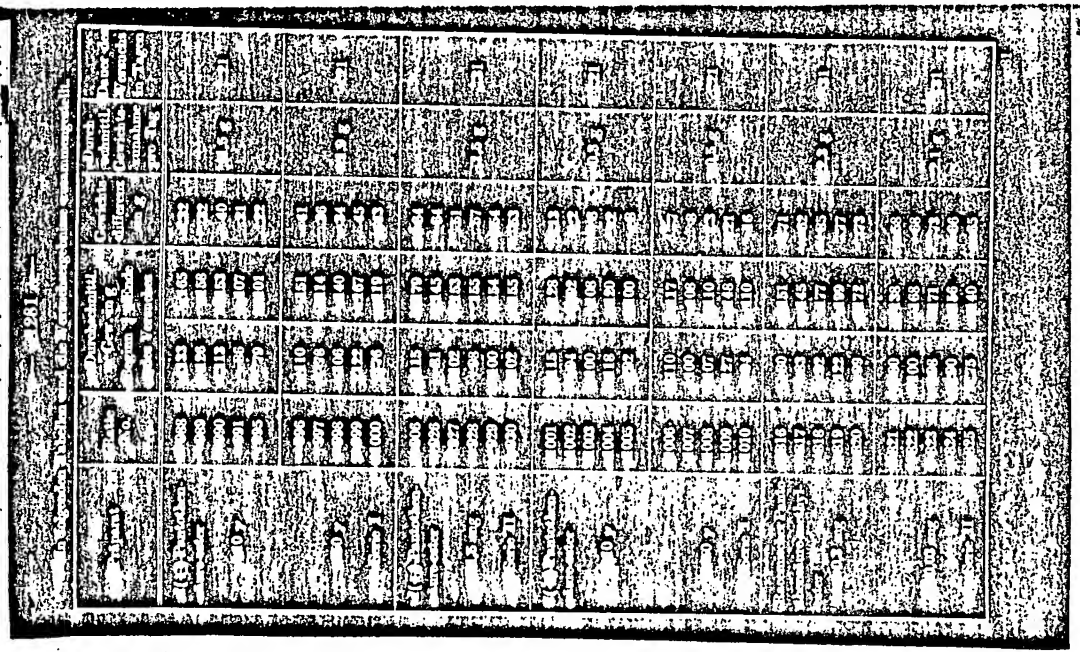
von *Hilde Pfaltz*

Zur biologischen Prüfung der Pantothensäure-Präparate wurde einerseits der Rattenwachstumstest, anderseits die Bestimmung der Reticulocytenzahlen herangezogen.

a) Wachstum. Für die Versuche wurden weisse Ratten eigener Zucht (Glaxostamm) verwendet. Sie wurden bis zum Alter von 4–5 Wochen auf Normalkost gehalten und wiesen nach dieser Zeit ein Gewicht von 50–60 g auf. Zur Vorbereitung für die Auswertungen wurden die Tiere bis zum Eintritt annähernder Gewichtskonstanz auf einer Grundkost folgender Zusammensetzung gehalten:

1) *H. K. Mitchell, H. H. Weinstock Jr., E. E. Snell, S. R. Stanbery, R. J. Williams*, Am. Soc. 62, 1776 (1940).
2) *R. J. Williams, H. K. Mitchell, H. H. Weinstock Jr., E. E. Snell*, Am. Soc. 62, 1784 (1940).
3) *E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, K. Folkers*, Am. Soc. 62, 1785 (1940).
4) Boll. Soc. ital. Biol. sper. 14, 378 (1939).
5) Z. physiol. Ch. 261, 103 (1939).





2. Reticulocyten. Die Bestimmung der Reticulocyten erfolgte nach der Vitalfärbemethode unter Verwendung von Brillant-Cresylblau, welches die Reticulocytenkerne dunkelblau anfärbt, während die Erythrocyten homogen bläulichgrün erscheinen. Die Blutentnahme erfolgte in allen Fällen einen Tag vor Verabreichung der Präparate, ferner 1, 2, bzw. 3 Tage nach deren Verabreichung. In jedem Ausstrich wurden die auf 1000 Erythrocyten entfallenden Reticulocyten gezählt. Die Schwankungen zwischen den einzelnen Tieren einer Versuchsreihe sind sehr erheblich. So wurden bei den Kontrolltieren Reticulocytenzahlen von 0,4—2,4 % gefunden. Es ergab sich somit die Notwendigkeit, rein statistisch an einer grossen Zahl von Kontrolltieren, bzw. mit Pantothensäure gefütterten Tieren, die Reticulocytenwerte zu erfassen. Ratten, die vom Vitamin B-Komplex Aneurin, Lactoflavin, Adermin, Nicotinsäure-amid, sowie eine Cholinzulage erhielten, wiesen im Alter von ca. 2 Monaten durchschnittlich einen Gehalt von 1,3 % Reticulocyten auf. Dieser Durchschnittswert wurde durch Blutuntersuchungen an über 100 Tieren ermittelt. Nach Zufuhr verschieden grosser Dosen von d(+)-Pantothensäure (siehe hierzu die oben beschriebenen Wachstumsversuche) wurden Reticulocytenwerte von durchschnittlich 3,4 % gefunden. Diese Zahl stellt den Durchschnitt von 30 Versuchstieren dar. Im günstigsten Fall war nach Verfütterung von d(+)-Pantothensäure ein Reticulocytenanstieg von 1,4 auf 5,2 % beobachtet worden.

Experimenteller Teil.

Herstellung der reinen d(−)- und l(+)-α-Oxy-β,β-dimethyl-butyrolactone (II) und (III).

20 g d,l-α-Oxy-β,β-dimethyl-butyrolacton wurden in 50 cm³ Methanol gelöst und ½ Stunde mit der Lösung von 27 g krystallisiertem Bariumhydroxyd in 500 cm³ Methanol unter Rückfluss gekocht. Dann wurde mit Kohlendioxyd neutralisiert und vom Bariumcarbonat abfiltriert. Das Filtrat wurde mit der heissen Lösung von Chininsulfat in Methanol genau ausgefällt, wozu etwa 60 g Chininsulfat in 800 cm³ Methanol nötig waren. Das Bariumsulfat wurde durch Zentrifugieren entfernt. Die Lösung gab beim Einengen zunächst 30 g rohes, schwerlösliches Chininsalz (A). Aus den Mutterlaugen wurden, wie früher beschrieben, 28 g rohes Chininsalz (B) erhalten. Aus den ersteren wurden durch Umkrystallisieren aus Methanol 26 g reines A-Salz gewonnen. Das rohe B-Salz wurde aus Methanol-Äther umkrystallisiert und gab 23 g gereinigtes B-Salz.

Zur Spaltung wurden 26 g A-Salz in 500 cm³ Methanol gelöst, mit der Lösung von 11 g Bariumhydroxyd in heissem Wasser versetzt und im Vakuum vom Methanol befreit. Dem Rückstand wurde durch Ausschütteln mit Chloroform das Chinin entzogen und Chloroformreste durch Ausschütteln mit Äther entfernt. Dann wurde mit Kohlendioxyd neutralisiert, vom Bariumcarbonat abfiltriert und die klare Lösung eingedampft. Der Rückstand wurde aus wenig Wasser durch Zusatz von Aceton umkrystallisiert und gab 10,5 g reines Bariumsalz (A) vom Smp. 198—200° (Zers.). Es zeigte eine spez. Drehung von $[\alpha]_D = -5{,}5° \pm 1°$ ($c = 2{,}8$ in Wasser).

Die 23 g Chininsalz (B) wurden analog mit Bariumhydroxyd gespalten. Das rohe Bariumsalz (10 g) wurde in 10 cm³ Wasser gelöst und mit 50 cm³ Aceton versetzt. Es fielen dabei rasch Krystall-

...handelnden Salze abgenutscht und mit Methanol gewaschen wurden. ... Ausbeuten 2,5 g und schmolzen nach einmaligem Umkrystallisieren aus Wasser mit Alkohol bei 220° korr. (Zers.). Es handelt sich um das ... saure Bariumsalz. Dasselbe Salz wird nämlich erhalten, wenn ... äquimolekulare Gewichtsmengen des (+)- und (−)-Salzes in Methanol gelöst ... zusammengegeben und mit einer Spur Wasser versetzt werden. Zur ... Analyse wurde an der Luft getrocknet.

(C10 ... Ba (Ber. ... Gef. ... 10)

Die Mutterlauge der genannten Krystalle wurde mit Aceton bis Eintritt zur Trübung versetzt und angeimpft, worauf sofort Krystallisation einsetzte, die durch längeres Stehen bei 0° und vorsichtigen Zusatz von Aceton möglichst vervollständigt wurde. Erhalten wurden ... Bariumsalz (B), das nach einmaligem Umkrystallisieren aus Wasser-Aceton bei 198—200° korr. (Zers.) schmolz. Die spez. Drehung ... [α]D ... (c = 1,615 in Wasser).

Zur Gewinnung des freien Lactons wurden 0,... Bariumsalz (B) in Wasser gelöst, mit Alkohol versetzt und mit etwas mehr als der berechneten Menge alkoholischer Salzsäure zersetzt. Das ausfallende Bariumchlorid wurde abfiltriert, das Filtrat im Vakuum eingedampft und der Rückstand durch zweimaliges Abdampfen mit etwas Benzol ... getrocknet. Der krystallisierte Rückstand wurde im Hochvakuum sublimiert. Das farblose, krystallisierte Sublimat schmolz roh bei 87—89° und zeigte eine spez. Drehung von [α]D ... 1,6° (c = 1,25 in Aceton). Einmaliges Umkrystallisieren aus Benzol-Petroläther brachte den Smp. auf 88—90°. Die spez. Drehung betrug [α]D ... (c = 1,43 in Aceton), bzw. [α]D ... 89,0° (c = 1,012 in Wasser).

Analog wurde das Bariumsalz (B) in freie (+)-Lacton (II) übergeführt. Das farblose Sublimat des Rohproduktes zeigte einen Smp. von 87—89° und eine spez. Drehung von [α]D ... 1,1° (c = 1,98 in Aceton). Einmaliges Umkrystallisieren aus Benzol-Petroläther ergab farblose Nadeln vom Smp. 89—90°. Die spez. Drehung betrug [α]D ... 1,5° (c = 1,71 in Aceton) bzw. [α]D ... 91,5° (c = 1,31 in Wasser).

Phenylhydrazid ... Dioxy-3,5-dimethyl-... butter-säure

... mg (= Aceton II) und 50 mg reines Phenylhydrazin wurden im Kohlendioxyd-Atmosphäre ½ Stunde auf 100° erwärmt. Im Kolbenkolben wurde bei 10° Badtemperatur ein geringer Vorlauf abgetrennt, dann destillierte unter 0,01 mm das Phenylhydrazid als farbloses Öl bei 150° Badtemperatur. Es konnte nicht zum Krystallisieren gebracht werden und zeigte eine spez. Drehung von [α]D ... 3,9° (c = 3,19 in Alkohol).

(+)-Pantothensäure-äthylester (IV, R = C_2H_5).

2 g (= 5 Lacton A) (II) und 0,9 g frisch im Vakuum destillierter β-Alanin-äthylester wurden in 3 ccm absolutem Alkohol 3 Stunden auf dem siedenden Wasserbad erhitzt. Dann wurde eingedampft und der Rückstand im Molekülkolben bei 0,01 mm destilliert. Ein Vorlauf wurde bis 130° Badtemperatur abgetrennt. Bei 135—140° Badtemperatur ging dann der gesuchte Ester als farbloses, dickes Öl über (1,75 g). Das Destillat wurde in absolutem Äther gelöst. Beim Stehen dieser Lösung schied sich eine Spur freies β-Alanin in farblosen Nadeln ab, die abfiltriert wurden. Das eingedampfte Filtrat wurde im Vakuum getrocknet und zeigte eine spez. Drehung von $[\alpha]_D^{20} = -36{,}8° \pm 0{,}5°$ (c = 1,68 in absolutem Alkohol).

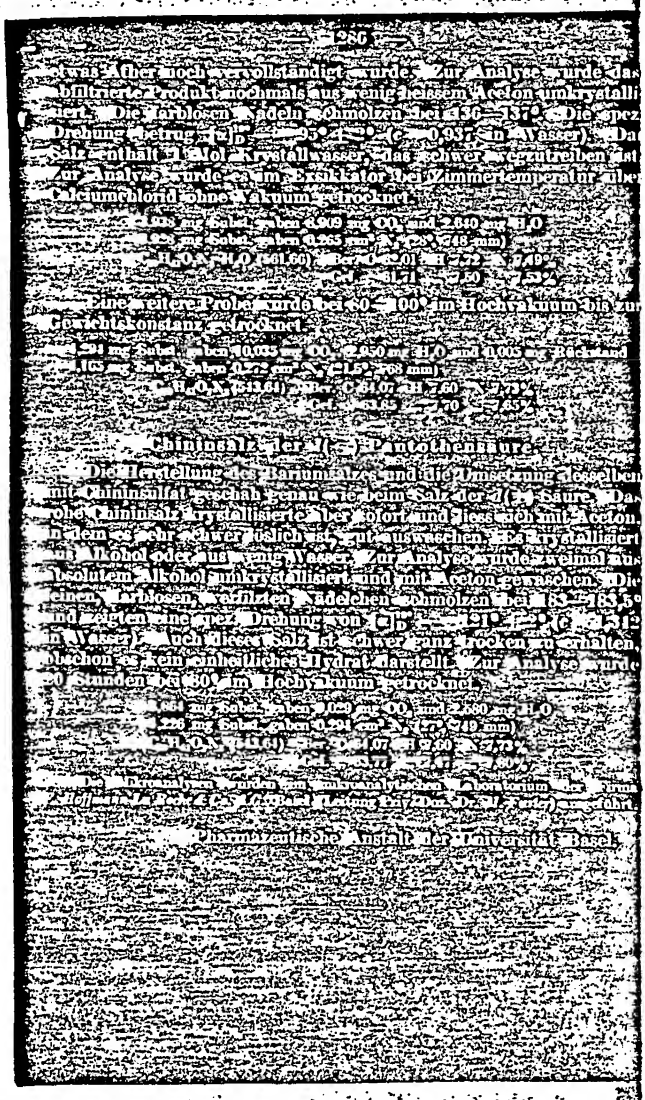
(+)-Pantothensäure-äthylester ($C_{11}H_{21}NO_5$).

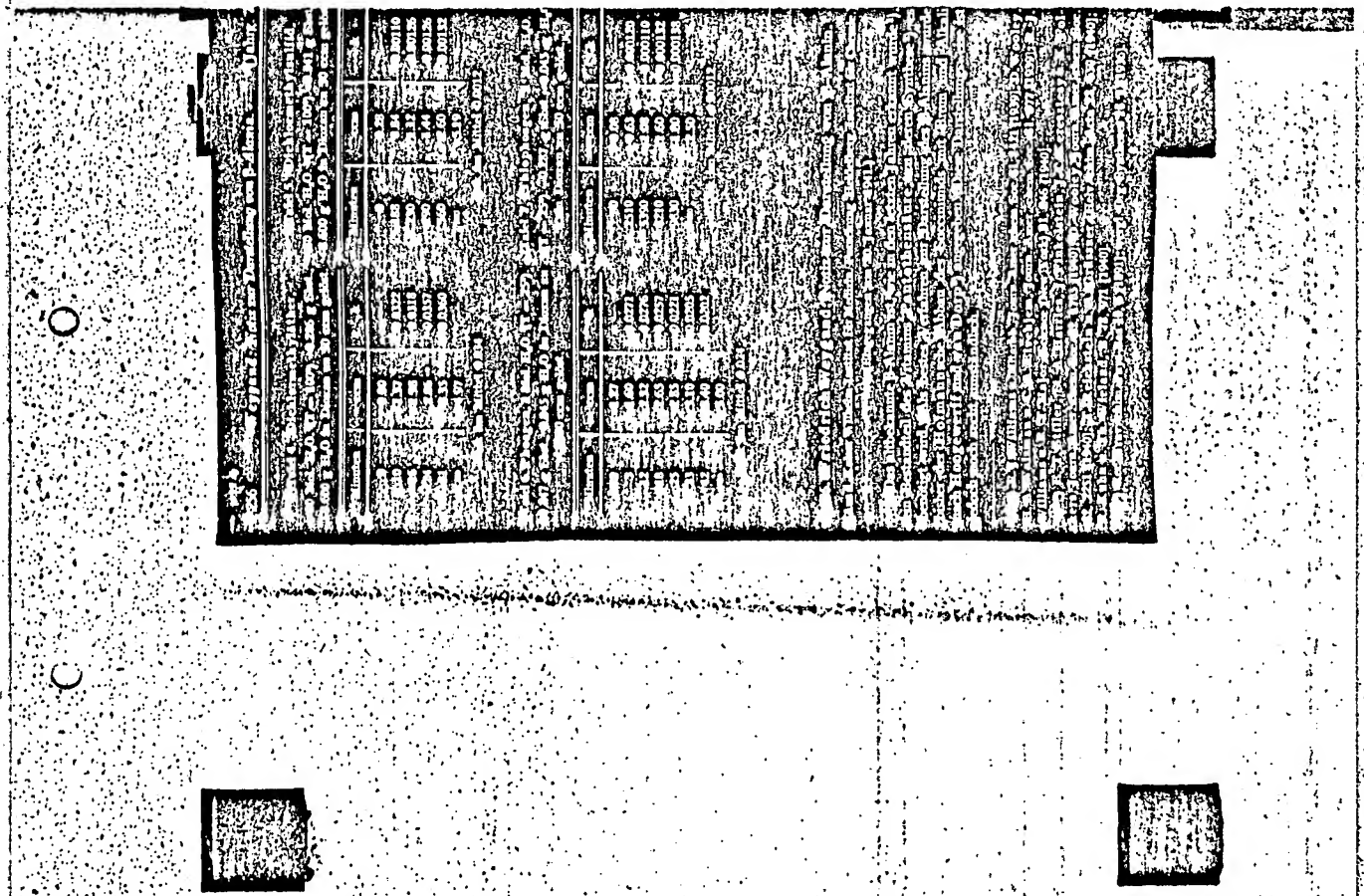
Der analog dargestellte Ester wurde ebenfalls als farbloses, in absolutem Äther lösliches Öl erhalten. Die spez. Drehung betrug $[\alpha]_D^{20} = -37{,}6° \pm 0{,}5°$ (c = 1,65 in absolutem Alkohol).

Chininsalz der (+)-Pantothensäure.

1 g (+)-Pantothensäure-äthylester (IV, R = C_2H_5) wurde unter Kühlung mit der berechneten Menge wässeriger Bariumhydroxydlösung versetzt und 3 Stunden bei Zimmertemperatur stehen gelassen. Dann wurde mit Kohlendioxyd neutralisiert, wobei über eine wägbare Menge von Bariumcarbonat entfiel. Die Lösung wurde im Vakuum zur Trockne eingedampft, der Rückstand in absolutem Alkohol aufgenommen, von wenig unlöslichen Flocken abfiltriert und mit so viel Aceton versetzt, bis eine weitere Fällung eintrat. Das als weisses Pulver ausgefallte Bariumsalz wurde abgenutscht, mit Aceton und Äther gewaschen und im Vakuum getrocknet. Die Ausbeute war fast quantitativ.

0,5 g des Bariumsalzes wurden in Methanol gelöst und heiss mit der heissen Lösung von Chininsulfat in Methanol genau ausgefällt, wozu 0,68 g Chininsulfat nötig waren. Das Bariumsulfat wurde durch Zentrifugieren entfernt und die klare Lösung im Vakuum eingedampft. Der Rückstand wurde mit wenig Aceton verflüssigt und 2 Tage bei 0° stehen gelassen. Es war dabei ein zäher Krystallbrei entstanden, der mit einer Mischung von Aceton und Äther verrieben wurde. Es wurde abgenutscht und mit denselben Lösungen gewaschen. Die rohen Krystalle wurden in wenig Wasser bei 0° gelöst, wobei ausser Spuren von Bariumsulfat noch wenig Krystalle in Nadeln ungelöst blieben. Es wurde über eine Spur Kieselgur filtriert, das klare Filtrat im Vakuum eingedampft, der Rückstand in wenig heissem Aceton gelöst und angerieben. Es trat sofort Krystallisation ein, die durch Stehen bei 0° und vorsichtigen Zusatz von





80. Polyoxyacyl-derivate des β-Alanins

von R. Reichstein und A. Grüssner.

(10. V. 40.)

Polyoxyacyl-derivate des β-Alanins haben in letzter Zeit erhebliches Interesse erlangt. So *Williams* und Mitarbeiter[1]) sowie *Wooley* und Mitarbeiter[2]) zeigten, dass Pantothensäure sich in seine alphalactische Dioxysäure und β-Alanin spalten lässt. Die Isolierung und Reinigung natürlicher Pantothensäure bereitet ausserordentliche Schwierigkeiten[3]). Die vollständige Reinigung ist bis heute nicht gelungen. Trotzdem konnten *Williams* und Mitarbeiter[4]) durch Anwendung speziell ausgearbeiteter Untersuchungsmethoden zunächst die ungefähre Bruttoformel, sowie die funktionellen Gruppen festlegen und in jüngster Zeit die Konstitution im Sinne der Strukturformel (I) aufklären[5]):

Viele biologische Fragen, die wegen der schweren Isolierung und Reinigung dieser interessanten Substanz heute noch ungelöst sind, dürften nun bald durch Verwendung synthetischen Materials abgeklärt werden. Die Herstellung von Stoffen vom Typus der Pantothensäure, also von Dioxyacyl-derivaten des β-Alanins ist in letzter Zeit bereits in der Literatur erwähnt worden. So schreiben *Wooley* und Mitarbeiter[2]), dass sie die durch Spaltung von natürlicher Pantothensäure erhaltene Dioxysäure wieder mit β-Alanin in aktiver Pantothensäure vereinigen konnten. *Subbarow* und *Rane*[6]) geben an, dass sie aus 2,4-Dioxy-valeriansäure mit β-Alanin ein Derivat erhielten, das an hämolytischen Streptococcen die Wirksamkeit der Pantothensäure zeigte. In beiden Fällen wurde zur Synthese die entsprechende Dioxysäure in ihr acetyliertes Chlorid übergeführt, dieses mit β-Alanin-methylester umgesetzt und das Reaktionsprodukt alkalisch verseift. Diese Methode ist für präparative Zwecke nicht günstig, besonders weil die Herstellung der substituierten Säurechloride umständlich ist und schlechte Ausbeuten liefert.

[1]) *R. W. Williams, T. A. Rinehart & A. L. Patterson*, Am. soc. **61**, 1421 (1939).

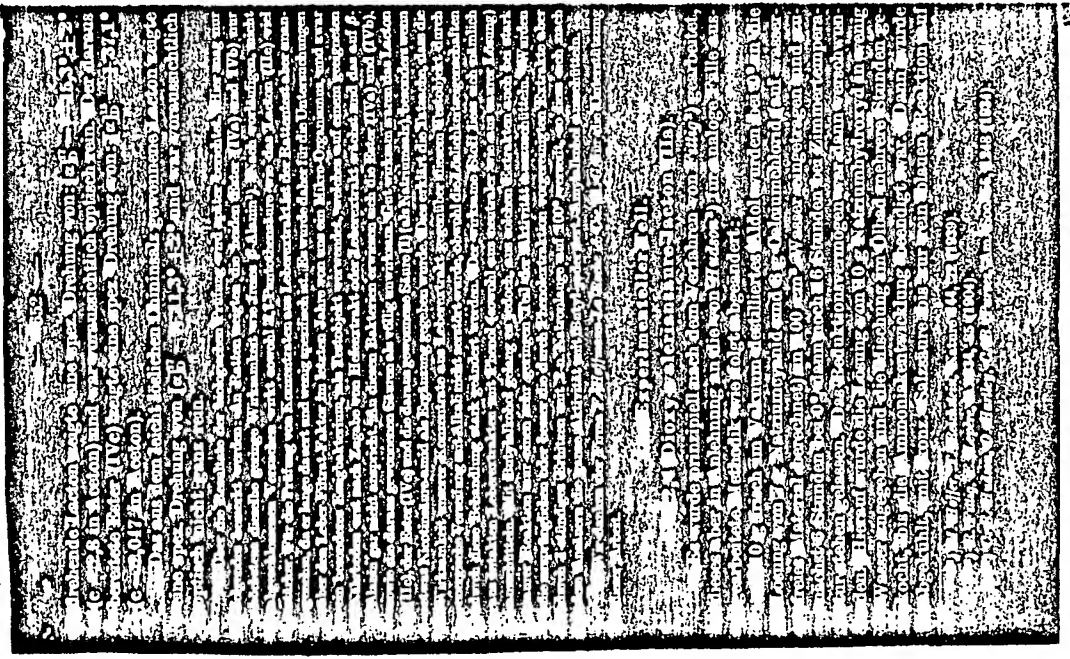
[2]) *D. W. Wooley*, Am. soc. **61**, 777 (1939).

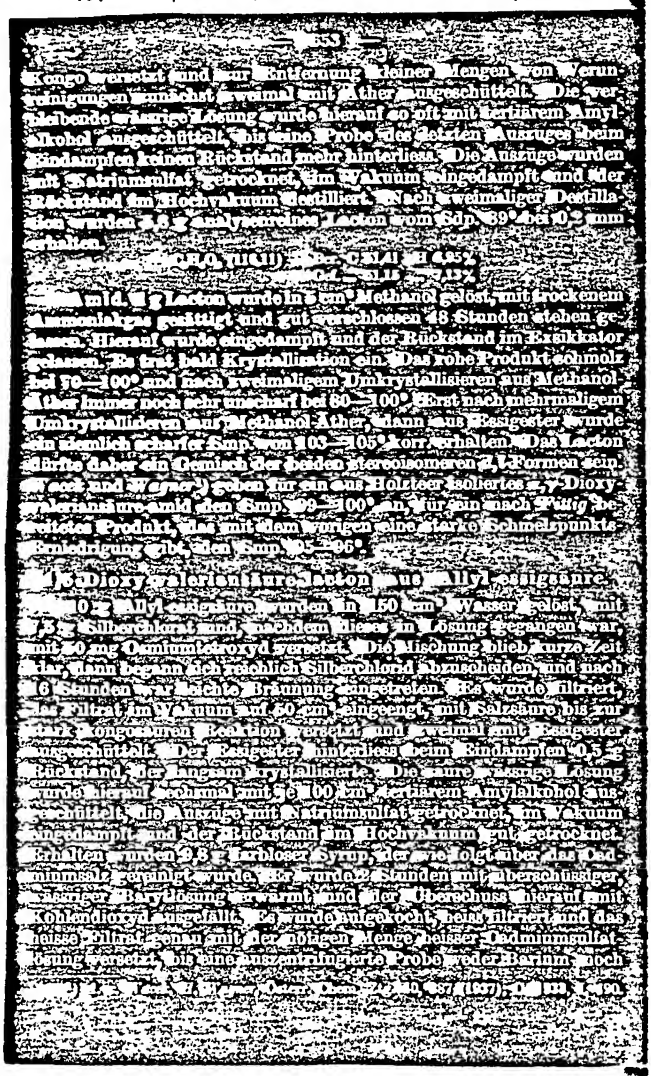
[3]) *R. W. Williams, A. L. Patterson, E. L. Tollenaar & A. Weinstock*, Am. soc. **61**, 1844 (1939). Frühere Arbeiten siehe dort.

[4]) *R. W. Williams & A. L. Patterson*, Am. soc. **61**, 778 (1939).

[5]) *R. W. Williams, A. L. Patterson & A. Weinstock*, Am. soc. **62**, 1213 (1940).

[6]) *Y. Subbarow & S. Rane*, Am. soc. **61**, 1610 (1939).





Sulfat-Ionen enthielt. Dann wurde über wenig Kohle abgesaugt und das klare Filtrat im Vakuum vollständig eingedampft. Der Rückstand wurde in heissem Methanol gelöst, durch Filtration von wenig anlöslichem Material befreit und bis zur Kristallisation stehen gelassen. Beim Impfen trat diese sofort ein. Die Kristalle wurden abgesaugt und mit Methanol und Äther gewaschen. Die Ausbeute betrug 3 g. Zur Analyse wurde eine Probe aus Wasser-Methanol umkristallisiert und im Hochvakuum bei 100° getrocknet. Das Salz schmilzt bei raschem Erhitzen bei etwa 193° unter Zersetzung und wird hierauf wieder fest. Bei langsamem Erhitzen tritt keine Schmelze, sondern nur allmähliche Zersetzung ein.

[illegible] (276,69) [illegible] 2,72 [illegible] 4,79 [illegible] Cl 29,69 %

[illegible] (276,69) [illegible] 1,69 [illegible] 3,14 [illegible] 28,15 %

Das Cadmiumsalz wurde in heissem Wasser gelöst und mit Schwefelwasserstoff zerlegt. Das Cadmiumsulfid wurde hierauf über wenig Kohle abgesaugt, das Filtrat im Vakuum eingedampft und der Rückstand zweimal im Hochvakuum destilliert. Es wurden 3,2 g farbloses Öl erhalten vom Sdp. 100° bei 0,1 mm. Grössere Mengen werden einfacher nach der Vorschrift von [illegible] hergestellt. Das [illegible] stellte [illegible] von [illegible] dar.

7,2,5-Dioxy-valeriansäure-lacton (IIb).

Dieses Lacton wurde in geringer Abänderung einer Vorschrift, die amt von der Firma *F. Hoffmann-La Roche & Co.*, Basel, zur Verfügung gestellt wurde, wie folgt bereitet:

100 g [illegible]-Chlorpropyl-brom-malonsäure-diäthylester) wurden in 100 ccm 96-proz. Alkohol gelöst und mit 300 g 33,3-proz. Natronlauge versetzt. Beim Umschütteln ging der Ester zunächst mit schöner Farbe in Lösung, dann erstarrte alles unter leichter Erwärmung zu einem dicken Kristallbrei. Es wurden 200 ccm Wasser zugegeben und die Mischung 12 Stunden unter Rückfluss gekocht. Hierauf wurde nochmals mit 100 ccm Wasser versetzt und der Alkohol vollständig abdestilliert. Nach dem Erkalten wurde mit konz. Salzsäure bis zur stark kongosauren Reaktion versetzt und unter Rückfluss so lange gekocht, bis die Gasentwicklung beendigt war. Dann wurde im Vakuum zur Trockne gedampft, der Rückstand sechsmal mit warmem Methylalkohol ausgezogen und diese Auszüge eingedampft. Der Rückstand wurde jeweils nochmal mit warmem Essigester ausgezogen, die Lösung filtriert, im Vakuum eingedampft und der Rückstand im Hochvakuum destilliert. Nach mehrmaliger Fraktionierung wurden 23 g farbloses Öl vom Sdp. 70° bei 0,1 mm oder 125° bei 10 mm Druck erhalten.

[illegible] (1909).

[illegible] (1913).

Das Amid krystallisierte gut, war aber äusserst hygroskopisch. Zur Charakterisierung besser geeignet ist das

p-Phenylhydrazid. 0,3 g 4,2,6-Dioxy-valeriansäure-lacton wurden mit 0,44 g Phenylhydrazin in 5 ccm absolutem Alkohol 1 Stunde unter Rückfluss gekocht. Die Lösung färbte sich leicht orange. Hierauf wurde im Vakuum eingedampft und der Rückstand mit Äther bis zum Auftreten der ersten Trübung versetzt. Sehr bald trat Krystallisation ein. Die Krystalle wurden mit Äther gewaschen und aus Alkohol-Äther umkrystallisiert. Die farblosen Nadeln schmolzen bei 106—107° korr. Zur Analyse wurde bei 0,0005 mm und 70° Blocktemperatur sublimiert.

[illegible] (224,26) [illegible] 0,4891 4,719 mg 12,49%
[illegible] 0,4711 4,725 12,77%

3,5-Oxy-2,2-dimethyl-butyrolacton (IIc).

Dieses Lacton wurde, von *Glaser*[1]) aus 3-Oxy-2,2-dimethyl-propion-aldehyd[2]) mittelst der Cyanhydrin-Reaktion bereitet. Wir benützten hierzu die bei der Herstellung von (IIa) beschriebene Modifikation. Das so bereitete Lacton destillierte im Vakuum von 11 mm bei 130°. Es erstarrte sofort und schmolz roh bei 76—78°. *Glaser* gibt einen Smp. von 85° an. Da das Produkt aber sehr hygroskopisch ist, sollte auf diesen Unterschied kein zu grosser Wert gelegt werden. Das Phenylhydrazid krystallisierte bisher nicht. Ebenso wenig gelang es, mit Diphenylhydrazin, *p*-Nitrophenylhydrazin und Hydrazin krystallisierte Derivate zu bereiten. Leicht krystallisiert hat bisher nur das

Amid. Dieses wurde wie das von (IIa) hergestellte und aus Methanol-Äther umkrystallisiert. Es schmolz bei 124—125° korr. Zur Analyse wurde im Hochvakuum bei 125° Blocktemperatur sublimiert.

[illegible] (117,11) [illegible] 0,4869 [illegible] 1,340 [illegible] 12,24%
[illegible] 0,4747 [illegible] 1,340 [illegible] 12,24%

Spaltung in optische Antipoden. 3 g Lacton wurden in 7 ccm Wasser gelöst und mit der Lösung von 3,9 g Chinin in 7 ccm Alkohol 6 Stunden unter Rückfluss gekocht. Hierauf wurde der Alkohol im Vakuum abdestilliert, die trübe wässrige Lösung zur Entfernung von Chinin zweimal mit Äther ausgeschüttelt und im Vakuum auf ein kleines Volumen eingeengt. Es krystallisierten 1,5 g Salz vom Smp. 185—186° in langen Prismen. Dieses Salz wurde aus Wasser-Methanol umkrystallisiert und gab 1,2 g Krystalle vom Smp. 186—187° (Salz A). Die wässrigen Mutterlaugen wurden im Vakuum ganz eingedampft und der Rückstand zweimal aus Methanol-Äther (1:8) umkrystallisiert. Es wurden 1,3 g wollige Nadeln vom Smp. 174—175° erhalten (Chininsalz B). Aus den letzten Mutterlaugen, die noch freies Lacton enthielten, konnten durch nochmaliges Kochen mit Chinin weitere Mengen der beiden Salze erhalten werden.

[illegible] (117,11) [illegible] 0,4869 [illegible] 1,340 [illegible] 12,24%

Linksdrehendes Lacton. 2 g Chininsalz (A) vom Smp. 86—187° (korr.) wurden in Methanol-Wasser gelöst und mit der wäßrigen Lösung von 2,2 g Bariumhydroxyd zersetzt. Das ausgefällte Chinin wurde durch Ausschütteln mit Chloroform und Äther entfernt. Aus der wäßrigen Lösung wurde das Bariumion mit Schwefelsäure ganz genau ausgefällt. Nach Filtration über eine Spur Kohle wurde die klare wäßrige Lösung im Vakuum eingedampft und der Rückstand im Molekularkolben bei 0,01 mm Druck und 100° Badtemperatur sublimiert. Erhalten wurden 80 mg Lacton, das sofort auskristallisierte, aber sehr hygroskopisch war. Es schmolz bei 80—85°. Aus Äther-Pentan ließ es sich umkristallisieren. Die spez. Drehung einer umkristallisierten Probe betrug: [illegible] (c = 2,80 in Aceton).

[illegible]

Amid des linksdrehenden Lactons. 40 mg linksdrehendes Lacton wurden wie bei der inaktiven Verbindung ins Amid überführt. Dieses wurde aus Methanol-Äther umkristallisiert und schmolz bei 124—124,5°. Die Mischprobe mit dem gleichschmelzenden DL-Amid schmolz bei 118—120°.

Rechtsdrehendes Lacton. 2 g Chininsalz (B) vom Smp. 176—177° wurden ganz wie das Salz (A) zerlegt. Das erhaltene Lacton wurde zweimal im Hochvakuum sublimiert und schmolz bei 78—80° nach vorherigem Sintern bei 70°. Die spez. Drehung betrug: [illegible] (c = 1,68 in Aceton).

[illegible]

Amid des rechtsdrehenden Lactons. Dieses wurde wie bei den anderen Amiden bereitet. Nach Sublimation und Umkristallisieren aus Methanol-Aceton-Äther schmolz es bei 124—124,5°. Es zeigte keine merkbare optische Drehung. Sowohl bei Natriumlicht wie bei grünem Quecksilberlicht wurde [illegible] (c = 1,68 in Methanol) gefunden.

2,4-Dioxy-3-chloro-3-isopropyl-3-alanin-methylester (Va). 2 g 2,4-Dioxy-3-chloro-3-isopropyl-3-alanin (IIa) wurden in 2 ccm Methanol gelöst und in das siedende Gemisch die Lösung von 0,8 g Natrium in Methanol langsam eingetropft. Anschließend wurde noch 1 Stunde unter Rückfluß gekocht. Dann wurde im Vakuum eingedampft und der Rückstand im Molekularkolben bei 0,001 mm destilliert. Bei einer Badtemperatur bis 100° wurde zunächst ein [illegible]

kleiner Vorlauf abgetrennt. Die Hauptmenge ging bei 135—140° Badtemperatur über. Es wurden 1.2 g farbloses, dickes Öl erhalten.

$C_{11}H_{21}O_4N$ (231.28) Ber. C 57.12 H 9.15 N 6.06%
Gef. „ 56.48 „ 9.39 „ 6.58%

Verseifung. Zur biologischen Prüfung wurde eine Probe wie folgt verseift: 50 mg Ester wurden mit der Lösung von 20 mg Natriumhydroxyd in 2.5 cm³ Wasser 6 Stunden bei Zimmertemperatur stehen gelassen. Dann wurde mit Salzsäure genau neutralisiert und direkt zur Prüfung verwendet.

β-[2,3-Dioxy-valeroyl]-β-alanin-methylester (IVb).

Der Ester wurde, genau wie beim 2,4-Dioxy-derivat beschrieben, gewonnen. Zur Analyse wurde im Molekularkolben bei 0.001 mm und 135° Badtemperatur destilliert. Der Ester stellt ein farbloses, dickes Öl dar.

Analog wurde der entsprechende Äthylester bereitet.

$C_{12}H_{23}O_4N$ (245.30) Ber. C 58.75 H 9.45 N 5.71%
Gef. „ 58.00 „ 9.09 „

Auch für biologische Versuche wurde wiederum eine Probe alkalisch verseift.

β-[2,4-Dioxy-β,β-dimethyl-butyroyl]-β-alanin-methylester (IVc).

(β-Pantothensäure-methylester.)

2.2 g 4-Oxy-β,β-dimethyl-butyrolacton und 2.5 g β-Alanin-methylester wurden in 8 cm³ Methanol 24 Stunde unter Rückfluss gekocht. Dann wurde im Vakuum eingeengt und der Rückstand im Molekularkolben im Hochvakuum destilliert. Unter 0.001 mm Druck wurde bis 100° Badtemperatur ein kleiner Vorlauf abgetrennt. Die zähwerdende Substanz ging bei einer Badtemperatur bis 130° vollständig als farbloses, dickes Öl über.

$C_{10}H_{19}O_5N$ (233.26) Ber. C 51.49 H 8.22 N 6.00%
Gef. „ 51.15 „ 7.42 „ 6.72%

Eine Probe des Esters wurde für biologische Versuche wie bei dem Homologen beschrieben, alkalisch verseift.

Optisch aktive Formen. Die optisch aktiven 4-Oxy-β,β-dimethyl-butyrolactone wurden genau so mit β-Alanin-methylester umgesetzt. Der aus dem linksdrehenden Lacton (α_D = −15.3°) erhaltene Ester (IVc) zeigte eine spez. Drehung von (α_D = −37.1 ± 3.7°; (c = 2.017 in Aceton). Ob teilweise Racemisierung eingetreten ist, soll später geprüft werden.

Herrn Prof. Dr. Tadeus Reichstein danken wir für sein Interesse an dieser Arbeit.

Pharmazeutische Anstalt der Universität, Basel.

CONSOLIDATED VULTEE AIRCRAFT CORPORATION

STINSON DIVISION
WAYNE, MICHIGAN

July 15, 1946

Mr. Brothman, Chief Engineer
A. BROTHMAN AND ASSOCIATES
114 East 32 Street
New York 16, New York

Dear Mr. Brothman:

Your inquiry about the four-place Stinson "Voyager 150" was welcomed here as further proof that the people who fly want an airplane with speed, utility, and load carrying capacity. Because Stinson engineers kept these requirements before them, the "Voyager 150" meets all of your expectations for a postwar plane.

The "Voyager 150" takes off in 550 feet, climbs at 770 feet per minute, and cruises at 125 miles an hour. The range is more than 600 miles, and the useful load is 944 pounds. Powered by a six cylinder horizontally opposed Franklin engine, the "Voyager" can take off from short fields carrying capacity loads. In a word, it's a working airplane that will provide you with fast, direct and economical transportation.

The price of the "Voyager 150" is $5495 at the factory with the two-way radio, two landing lights, the antenna and fixed loop installed. Since there is a Stinson representative in the territory where you reside, we are forwarding your inquiry to him.

Thanks for your interest in Stinson and the "Voyager 150".

Sincerely yours,

STINSON, Division of
Consolidated Vultee Aircraft Corp.

Larry Cooper

Larry Cooper
General Sales Manager

LC:dd
Encl:

Photocopies

Pyridoxine (B6)

#1
6/6/

Patented July 8, 1941

2,248,078

SEP 2 '44 B

UNITED STATES PATENT OFFICE

2,248,078

PROCESS OF PREPARING VITAMIN B₆

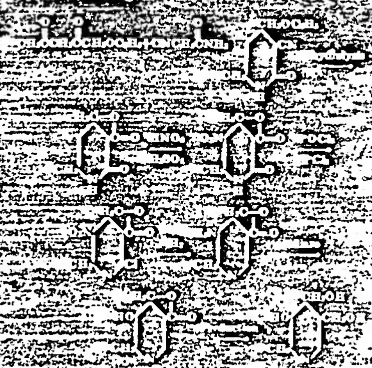
Stanton A. Harris, Westfield, N. J., assignor to Merck & Co., Inc., Rahway, N. J., a corporation of New Jersey

No Drawing. Application December 27, 1938, Serial No. 247,945

[illegible] Claims. (Cl. 260—295)

This invention relates to a process of preparing vitamin B_6 and related compounds, and to new intermediate products made and employed in such process.

I have discovered that these compounds may be synthesized by reacting ethoxyacetylacetone and cyanoacetamide to form 3-cyano-4-ethoxymethyl-6-methylpyridone-2, hydrolyzing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2, treating the latter compound with nitric acid to form the lactone of 3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridone-2, chlorinating the latter compound to form the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine, reducing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, or alternatively, by reducing the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine to the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, and reducing the latter compound to the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, diazotizing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine, and reducing the latter compound to form vitamin B_6. These steps may be represented by the following:



The following example illustrates one method of carrying out the present invention, but it is to be understood that the example is given by way of illustration and not of limitation.

Example

Sixty-five and three tenths gms. of cyanoacetamide are dissolved in 500 cc. of hot 95% alcohol and 93.1 gms. of ethoxyacetylacetone are added. Twenty-five cc. of piperidine are then added with shaking, whereupon the mixture becomes warm. The solution is cooled and allowed to stand overnight, again cooled, and filtered. The crystals are washed with 95% alcohol and a yield of 92 gms. or 81% of white crystals is obtained having a melting point of 200–202° C. Upon recrystallization from boiling 95% alcohol, crystals of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 are obtained, which have a melting point of 202.5° C.

Fifteen gms. of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 are mixed with 125 cc. of concentrated hydrochloric acid and heated at 120–125° C. for four hours. The reaction mixture is poured into 400 cc. of a mixture of water and ice, whereupon crystals of the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 appear. The mass is filtered and washed with water, the dried product weighing 11.1 gms. or about 87% yield. Upon recrystallization from water the crystals have a melting point of 320° [illegible] C. (uncorrected).

Alternatively, the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 may be obtained by refluxing 93 gms. of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 for three hours with 1120 cc. of 50% sulfuric acid, the temperature of the liquid being 120° C. The reaction mixture is poured into 2.5–4.0 liters of water and placed in an ice room overnight. The next day, the crystals are filtered off, washed well with water, alcohol, and ether, and dried at a temperature of 65–80° C. The yield is 70.5 gms. or 88.2% of theory.

Twenty-eight gms. of the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 are dissolved in 82 cc. of concentrated sulfuric acid, the solution is cooled, and added to an ice cold mixture of 124 cc. of concentrated sulfuric acid and 32 cc. fuming nitric acid (sp. gr. 1.5). The mixture warms spontaneously, reaching a temperature of 35–45° C. After this temperature starts to fall, the mixture is cooled to 25° C. and poured onto crushed ice, the final volume being about 1 liter. A yellow solid forms immediately, which is filtered off and dried at 65° C. The yield of the lactone of 3-carboxy-4-hydroxy-

[illegible]ymethyl-5-nitro-4-methylpyridone-3 is 20.5 gms. (over 63.5%, m.p. on recrystallization from water, 2% acetic at 270-280° C., with decomposition.

Fifteen and three tenths gms. of the lactone of 2-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridone-3, 50 cc. of phosphorus oxychloride, and ten grams of phosphorus pentachloride (75%) are mixed and refluxed until solution occurs, which requires about ½ of an hour. The phosphorus oxychloride is distilled off under vacuum, whereupon a solid separates. The solid is dissolved in benzene, filtered and precipitated by the addition of petroleum ether. The total yield of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine is 13.5 gms. or 77% of theory. It may be recrystallized from benzene and ethyl acetate and has a melting point of 176-178° C.

Twelve and twenty-eight hundredths gms. of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine are dissolved in 150 cc. of a mixture of ethyl acetate and 95% of ethyl alcohol, 10 gms. of 5% palladium on barium carbonate and 9.5 gms. of platinum oxide are added as a catalyst and the mixture is hydrogenated under about two atmospheres pressure. The reaction proceeds smoothly and takes up the full four mols of hydrogen in about one hour. The solution is filtered and the solvent removed by evaporation. The residue is extracted with a mixture of water and chloroform, the chloroform layer is separated, and the chloroform removed. The residue is recrystallized from ethyl acetate, and is the lactone of 2-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine-3, m.p. 228-230° C. The picrate of this compound is made by mixing alcohol solutions of the base and picric acid, 98% is filtered and recrystallized from water or alcohol. The picrate has a melting point of 240° C. with decomposition. Alternatively, 7.63 gms. of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine is dissolved in 100 cc. of glacial acetic acid, 0.5 gm. platinum oxide added and the mixture shaken with hydrogen at three atmospheres pressure until three molecular equivalents are absorbed. The reduction is stopped, the mixture filtered, stirred and recrystallized from glacial acetic acid. The total yield of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine is 3.21 gms. or 49% of theory. It may be recrystallized directly from glacial acetic acid or from dilute hydrochloric acid by dilution and has a melting point of 308-310° C.

Five and eighty-five hundredths gms. of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine is suspended in 250 cc. of water, treated with 10 gms. of sodium and potassium carbonate in a 5 to 1 ratio, 0.5 gm. of 5% palladium on barium carbonate as a catalyst and shaken with hydrogen at 3.5 atmospheres pressure and 70° C. until the theoretical quantity is absorbed. The solution is filtered from the catalyst and cooled to precipitate any unreacted 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine-3. Additional material is obtained by evaporation of the aqueous solution. The total yield of the lactone of 2-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine is 4.1 gms. or 87.5% of theory. The picrate, prepared in the usual manner, melts at 270° C. and is recrystallized from ethyl acetate.

[illegible] of the lactone of 2-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine is dissolved in 20% hydrochloric acid, 0.5 gm. of 5% palladium on barium carbonate added and the mixture shaken with hydrogen at about 3 atmospheres pressure and about 70° C. until the theoretical quantity is absorbed. The solution is filtered from the catalyst and the [illegible] of 2-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine-3 is [illegible]

[illegible] chloride. The water is removed by evaporation, and the lactone of 2-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine is obtained by extractions with alcohol, M.P. 272-3° C. The latter compound is dissolved in anhydrous acetic acid and sodium amalgam is added until reaction is complete. The acetic solution is stirred with concentrated hydrochloric acid and refluxed for three hours. The solution is then concentrated in vacuo and the hydrochloride of vitamin B6 is extracted with alcohol and crystallized by the addition of acetone. If desired, the vitamin B6 free base can be obtained from the hydrochloride, and has the formula 3,4-di(hydroxymethyl)-5-hydroxy-6-methylpyridine.

Alternatively, the lactone of 2-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine is dissolved in 20% hydrochloric acid and warmed on a boiling water bath. Granulated tin is added and the mixture heated for one hour. The solution is evaporated to dryness and the residue dissolved in water and treated with hydrogen sulphide to remove the tin. The filtrate is again evaporated to dryness and the vitamin B6 hydrochloride is recrystallized from alcohol and acetone.

Alternatively, the lactone of 2-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine is dissolved in water and reduced with hydrogen in a high pressure bomb at 175° C. with copper chromite as the catalyst. After cooling to room temperature the solution is filtered from the catalyst and evaporated to dryness to obtain vitamin B6.

Modifications may be made in carrying out this invention without departing from the spirit and scope thereof.

I claim:

1. In the process of preparing vitamin B6, the steps which comprise reacting chloroacetylacetone and cyanoacetamide to form 3-cyano-4-methoxymethyl-6-methyl-pyridone-2, and converting the latter by a series of reactions into vitamin B6.

2. In the process of preparing vitamin B6, the steps which comprise hydrolyzing 3-cyano-4-methoxymethyl-6-methylpyridone-2 to form the lactone of 2-carboxy-4-hydroxymethyl-6-methylpyridone-3, and converting the latter by a series of reactions into vitamin B6.

3. In the process of preparing vitamin B6, the steps which comprise treating the lactone of 2-carboxy-4-hydroxymethyl-6-methylpyridone-3 with nitric acid to form the lactone of 2-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridone-3, and converting the latter by a series of reactions into vitamin B6.

4. In the process of preparing vitamin B6, the steps which comprise chlorinating the lactone of 2-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridone-3 to form the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine, and converting the latter by a series of reactions into vitamin B6.

5. In the process of preparing vitamin B6, the steps which comprise reducing the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine to form the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, and converting the latter by a series of reactions into vitamin B6.

6. In the process of preparing vitamin B6, the steps which comprise reducing the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine to form the lactone of 2-carbo[illegible]

methylpyridine-5, chlorinating the latter compound to form the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, reducing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, dissolving the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine, and reducing the latter compound to form vitamin B6.

11. The lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine.

12. The lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine.

13. The lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine.

14. Compounds of the general formula

wherein R6 is a member selected from the group consisting of nitro, amino, and hydroxy, and R5 is a member selected from the group consisting of chlorine and hydrogen.

STANTON A. HARRIS.

Certificate of Correction

Patent No. 2,344,078. July 8, 1941.

STANTON A. HARRIS

It is hereby certified that errors appear in the printed specification of the above numbered patent requiring correction as follows: Page 2, second column, lines 17 and 18, claim 10, for the formula

read that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 27th day of April, A. D. 1943.

HENRY VAN ARSDALE,
Acting Commissioner of Patents.

Patented July 22, 1941 2,250,396

UNITED STATES PATENT OFFICE

...tion of gas. After ½ hour's standing the excess thionylchloride is distilled off under reduced pressure. The solid residue is rubbed on with a small quantity of ether and filtered with suction. The acidchloride-hydrochloride thus obtained is gradually introduced into 2 liters of 25% aqueous ammonia while stirring, whereby the acid amide precipitates at once and is filtered off with suction.

...00 parts of the 2-methoxy-quinaldine-4-carboxylic acid amide thus obtained are covered by pouring with 500 parts of phosphorus oxychloride and boiled for 2–3 hours while cooling under reflux, whereby gradually a clear brown solution is obtained. The excess phosphorus oxychloride is evaporated under reduced pressure and the oily residue is poured on to ice. It is now made alkaline 40 times by the addition of ammonia and the insoluble precipitate, formed, dissolved in methylenechloride. The methylenechloride solution is dried with potassium carbonate and the methylenchloride is evaporated from the dry solution. The remaining solid residue is distilled under reduced pressure. The 2-methoxy-quinaldine-4-carboxylic acid nitrile thus obtained distills under 3 mms. pressure at 150° C. as an oil which solidifies to crystals melting at 82° C.

...000 parts of this product are shaken with 10 parts of animal charcoal, 10 parts of palladium-chloride solution, 300 parts of concentrated hydrochloric acid and 1500 parts of water with hydrogen at room temperature until after the taking up of 2 mols of hydrogen no further hydrogen is taken up by it more. The solution is now freed from the animal charcoal by dilution with water, it is made strongly alkaline with sodium hydroxide solution and the oil precipitated is extracted with methylenechloride. The residue remaining after drying of the methylenechloride solution and the evaporation of the solvent is distilled under reduced pressure. The 2-methoxy-4-(3-hydroxymethyl-)-quinaldine thus obtained distils as a colourless liquid passing over at 150° C. under 3 mms. pressure.

...000 parts of 2-methoxy-4-(3-hydroxymethyl-)-quinaldine are dissolved in 800 parts of 4-normal hydrochloric acid and gradually treated, while stirring, with a solution of 25 parts of sodium nitrite in 150 parts of water at 60° C. The reaction takes place at once with the evolution of nitrogen. After cooling the mixture is made alkaline with ammonia, whereby the 2-methoxy-4-hydroxymethyl-quinaldine precipitates at once in white crystals, melting at 130° C. when recrystallised from benzene.

...parts of 2-methoxy-4-hydroxymethyl-quinaldine are dissolved in 300 parts of hydrochloric acid (specific gravity = 1.19) and heated for 1 hour on a water bath at 80° C. The hydrochloride of the acid is precipitated under reduced pressure. The residue is dissolved in water, the solution is saturated with potassium carbonate and the precipitated 2-methoxy-4-hydroxymethyl-quinaldine-6-carboxylic acid is filtered off with suction. It melts at 240° C. with decomposition.

...parts of 2-methoxy-4-hydroxymethyl-quinaldine-6-carboxylic acid are dissolved in 100 parts of water by the addition of 100 parts of 4-normal sodium hydroxide solution and the solution is evaporated to dryness under reduced pressure. The residue is dissolved in 200 parts of dimethylformamide and the solution is saturated with methylchloride. The sodium salt of the 2-methoxy-4-hydroxymethyl-quinaldine-6-carboxylic acid is filtered off with suction. The methylenechloride is evaporated from the dry solution and the residue is dissolved in 200 parts of dimethylformamide. 50 parts of methyl iodide are added and the mixture is heated for 2 hours at 100° C. in a closed vessel. The dimethylformamide is then evaporated under reduced pressure and the residue is poured on to ice. The precipitate is extracted with methylenechloride and the solution is dried with potassium carbonate. The methylenechloride is evaporated from the dry solution and the residue is distilled under reduced pressure. The 2-methoxy-4-methoxymethyl-quinaldine-6-carboxylic acid methyl ester thus obtained distils at 160° C. under 0.4 mm. pressure. It crystallises from petroleum ether in colourless crystals melting at 70° C.

...parts of 2-methoxy-4-methoxymethyl-quinaldine-6-carboxylic acid methyl ester are heated with 100 parts of 4-normal sodium hydroxide solution for 1 hour on a water bath at 80° C. The solution is then evaporated to dryness under reduced pressure and the residue is dissolved in 200 parts of dimethylformamide. The solution is saturated with methylchloride and the sodium salt of the 2-methoxy-4-methoxymethyl-quinaldine-6-carboxylic acid is filtered off with suction. The methylenechloride is evaporated from the dry solution and the residue is dissolved in 200 parts of dimethylformamide. 50 parts of methyl iodide are added and the mixture is heated for 2 hours at 100° C. in a closed vessel. The dimethylformamide is then evaporated under reduced pressure and the residue is poured on to ice. The precipitate is extracted with methylenechloride and the solution is dried with potassium carbonate. The methylenechloride is evaporated from the dry solution and the residue is distilled under reduced pressure. The 2-methoxy-4-methoxymethyl-quinaldine-6-carboxylic acid dimethyl ester thus obtained distils at 170° C. under 0.4 mm. pressure. It crystallises from petroleum ether in colourless crystals melting at 70° C.

...parts of 2-methoxy-4-methoxymethyl-quinaldine is introduced while cooling with ice into 10 parts of nitric acid (specific gravity = 1.5). The solution obtained is at once poured on to ice and the mixture is made alkaline with ammonia, whereupon the nitration product precipitates at first as a yellow oil which after some time solidifies to yellow-green crystals, which melt at about 65° C.

...2.8 parts of the above-mentioned nitration product are gradually introduced into 10 parts of a 66% solution of stannous chloride at 60° C. in concentrated hydrochloric acid. A tin-double salt precipitates, which is sucked off. From this salt the amino compound of the 2-methoxy-4-methoxymethyl-quinaldine is set free by means of concentrated sodium hydroxide solution and shaken out with methylenechloride. When worked up in the usual way this amino compound is obtained as slightly yellowish viscous oil which boils at 160° C. under 0.4 mm. pressure. It shortly after solidifies to crystals.

...part of the amino compound mentioned above is suspended in 250 parts of water, containing ½ part of barium hydroxide, and gradually treated, while permanently cooling with ice, with a solution of 2 parts of barium permanganate in 150 parts of water. Thereupon the mixture is heated for a short time, sucked off while hot from manganese dioxide, the manganese dioxide is several times extracted with boiling water and the united filtrates are concentrated to ½ of their volume under reduced pressure. The concentrated solution is shaken out with methylenechloride, the barium ions are precipitated from the aqueous solution by the addition of the required quantity of sulfuric acid as barium sulfate. The filtrate from the barium sulfate precipitate is evaporated to dryness under reduced pressure. The 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5,6-dicarboxylic acid is obtained after running on with acetone and filtration with suction as a yellow powder, which readily dissolves in water. The aqueous solution of this dicarboxylic acid yields a strong red coloration with ferrous sulfate. On heating carbon dioxide is split off and 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid (melting at 230° C.) is obtained. Its methyl ester boils under 3 mms. pressure at 155° C. The methyl ester forms needles at 129° C. (from alcohol).

...part of 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid is treated with 5 parts of thionylchloride. The substance dissolves with the evolution of gas and while standing for ½ hour standing at room temperature. The excess thionylchloride is evaporated under reduced pressure. The residue is covered by pouring with 10 parts of concentrated aqueous ammoniacal solution. One part of the carboxylic acid amide formed precipitates thereby. The above mixture is evaporated under reduced pressure and the solid residue is dried and then extracted with methylenechloride. After evaporation of the methylenchloride the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid amide is obtained in crystals melting at 130° C.

...part of this amide is boiled under reflux with ... parts of thionylchloride for ½ hour. Excess thionylchloride is distilled off and then the residue is evaporated with ... The residue is treated with ice water and ... extracted with ...

addition of ammonia until pH reaches 8 to 9. The ethereal solution is dried by potassium carbonate, the ether is evaporated and the residue is distilled. The 2-methyl-3-methoxy-4-methoxymethyl-5-cyanopyridine distils under 0.01 mm. pressure at a boiling point of 110° C. and has a melting point of 39° C.

6 Claims.

The process which comprises reacting 2-methoxy-quinaldine-4-carboxylic acid derivative of the group consisting of carboxylic acid halides and ester derivatives with ammonia to form the 2-methoxy-quinaldine-4-carboxylic acid amide, converting the latter into the corresponding 4-nitrile by the action of a dehydrating agent, transforming the 2-methoxy-4-aminomethyl-quinaldine by the action of a hydrogenating agent acting upon the 4-nitrile-methyl compound with ammonia and a catalyst of the platinum group of the 2-methoxy-4-aminomethyl-quinaldine obtained in the preceding operation, diazotizing the 2-methoxy-4-aminomethyl-quinaldine by treatment with nitrous acid, reducing the nitro compound obtained by the corresponding amino compound by the action of a reducing agent converting the amino compound into the diazonium salt by the action of nitrous acid, decomposing the diazonium salt into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid by heating in aqueous solution, transforming the 5-carboxylic group into the 5-carboxylic acid halide group by the action of a halogenating agent, acting upon the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide with ammonia and converting the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-amine by the action of a decomposing agent.

The process which comprises reacting 2-methoxy-quinaldine-4-carboxylic acid halide with ammonia to form the 2-methoxy-quinaldine-4-carboxylic acid amide, converting the latter into the corresponding 4-nitrile by the action of a dehydrating agent, transforming the 2-methoxy-4-aminomethyl-quinaldine by the action of a hydrogenating agent acting upon the 4-nitrile-methyl compound with ammonia and a catalyst of the platinum group of the 2-methoxy-4-aminomethyl-quinaldine obtained in the preceding operation, diazotizing the 2-methoxy-4-aminomethyl-quinaldine by treatment with nitrous acid, reducing the nitro compound obtained by the corresponding amino compound by the action of a reducing agent converting the amino compound into the diazonium salt by the action of nitrous acid, decomposing the diazonium salt into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid by heating in aqueous solution, transforming the 5-carboxylic group into the 5-carboxylic acid halide group by the action of a halogenating agent, acting upon the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide with ammonia and converting the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-amine by the action of a decomposing agent.

The process which comprises reacting 2-methoxy-quinaldine-4-carboxylic acid halide with ammonia to form the 2-methoxy-quinaldine-4-carboxylic acid amide, converting the latter into the corresponding 4-nitrile by the action of a dehydrating agent, transforming the 2-methoxy-4-aminomethyl-quinaldine by the action of a hydrogenating agent acting upon the 4-nitrile-methyl compound with ammonia and a catalyst of the platinum group of the 2-methoxy-4-aminomethyl-quinaldine obtained in the preceding operation, diazotizing the 2-methoxy-4-aminomethyl-quinaldine by treatment with nitrous acid, reducing the nitro compound obtained by the corresponding amino compound by the action of a reducing agent converting the amino compound into the diazonium salt by the action of nitrous acid, decomposing the diazonium salt into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid by heating in aqueous solution, transforming the 5-carboxylic group into the 5-carboxylic acid halide group by the action of a halogenating agent, acting upon the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide with ammonia and converting the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid halide into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-amine by the action of a decomposing agent.

A compound of the formula

wherein X stands for a substituent of the group consisting of carboxylic, carboxylic acid halide, carboxylic acid amide and nitrile groups.

A compound of the formula

wherein X stands for a substituent of the group consisting of carboxylic, carboxylic acid halide, carboxylic acid amide and nitrile groups.

A compound of the formula

A compound of the formula

A compound of the formula

Dieselben beginnen gegen 180° unter Bräunung zu sintern, und schmelzen gegen 240° zu einer trüben Flüssigkeit, die beim weiteren Erhitzen zu einer gelblichen, undurchsichtigen Masse erstarrt, alsdann noch nicht bei 270° wieder schmilzt und sich von 260° ab braunroth färbt. Der zur Analyse bestimmte Antheil wurde durch Umkrystallisiren aus etwa 150 Theilen kochendem Wasser in haarfeinen, schwach gelblichen Nadeln erhalten und im Vacuum über Schwefelsäure getrocknet:

0.1763 g Sbst.: 0.4020 g CO_2, 0.0971 g H_2O. — 0.1863 g Sbst.: 0.4275 g CO_2, 0.0983 g H_2O. — 0.2019 g Sbst.: 0.4597 g CO_2, 0.103 g H_2O. — 0.2097 g Sbst.: 0.4779 g CO_2, 0.1111 g H_2O. — 0.1492 g Sbst.: [illegible] ccm N (16°, 764 mm). — 0.2155 g Sbst.: 13.9 ccm N (10°, 774 mm).

$C_{10}H_9NO_2 + H_2O$.

Ber. C 62.18, H 5.69, N 7.25.

Gef. » 62.18, 62.58, 62.10, 62.15, » 6.12, 5.86, 5.69, 5.89, » 7.16, 7.22.

Die Substanz ist:

[illegible]-Methyloxyisocarbostyril, $C_6H_4 \lessgtr \begin{matrix} CO - NH \\ C(OH):C.CH_3 \end{matrix} + H_2O$;

sie löst sich nicht in verdünntem Ammoniak, leicht in fixen Alkalien mit gelber Farbe, wird daraus durch verdünnte Säuren oder Salmiak wieder niedergeschlagen und ziemlich leicht von heissem Alkohol aufgenommen.

Zur Bestimmung des Krystallwassers wurde die Substanz im Vacuum auf 100° bis zur Gewichtsconstanz erhitzt:

0.4341 g Sbst. verloren 0.0406 g.

$C_{10}H_9NO_2 + H_2O$. Ber. H_2O 9.33. Gef. H_2O 9.39.

Da die bei dieser Bestimmung hinterbliebene wasserfreie Substanz sich durch die lang andauernde Erhitzung ziemlich stark verfärbt hatte, wurde eine Portion der Substanz bei niedrigerer Temperatur entwässert und zwar wie folgt: Es wurden [illegible] g Substanz mit 50 ccm Xylol so lange, bis sich im Halse des Kolbens nicht mehr Wassertropfen condensirten, [illegible]. Der Körper war dabei nicht in Lösung gegangen und völlig farblos geworden. Nach dem Absaugen und Waschen mit Benzol wurde er bei 100° getrocknet.

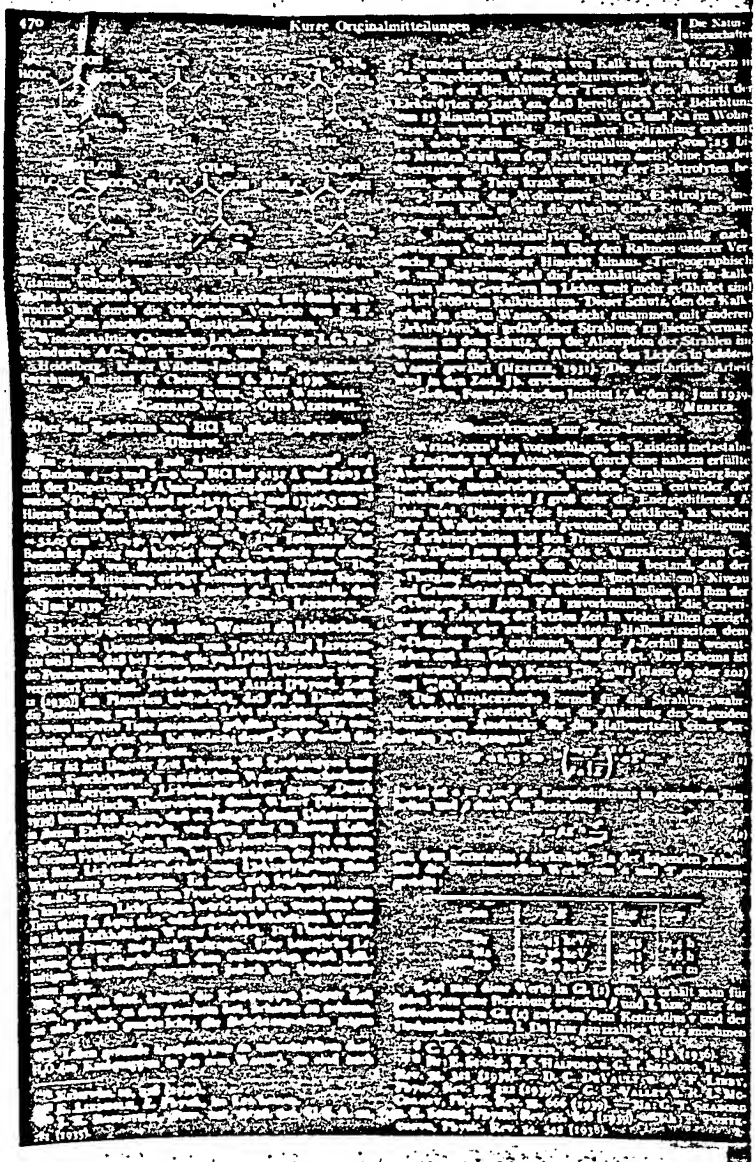
0.1615 g Sbst.: 0.4091 g CO_2, 0.0788 g H_2O. — 0.2060 g Sbst.: 13.9 ccm N (16°, 768 mm).

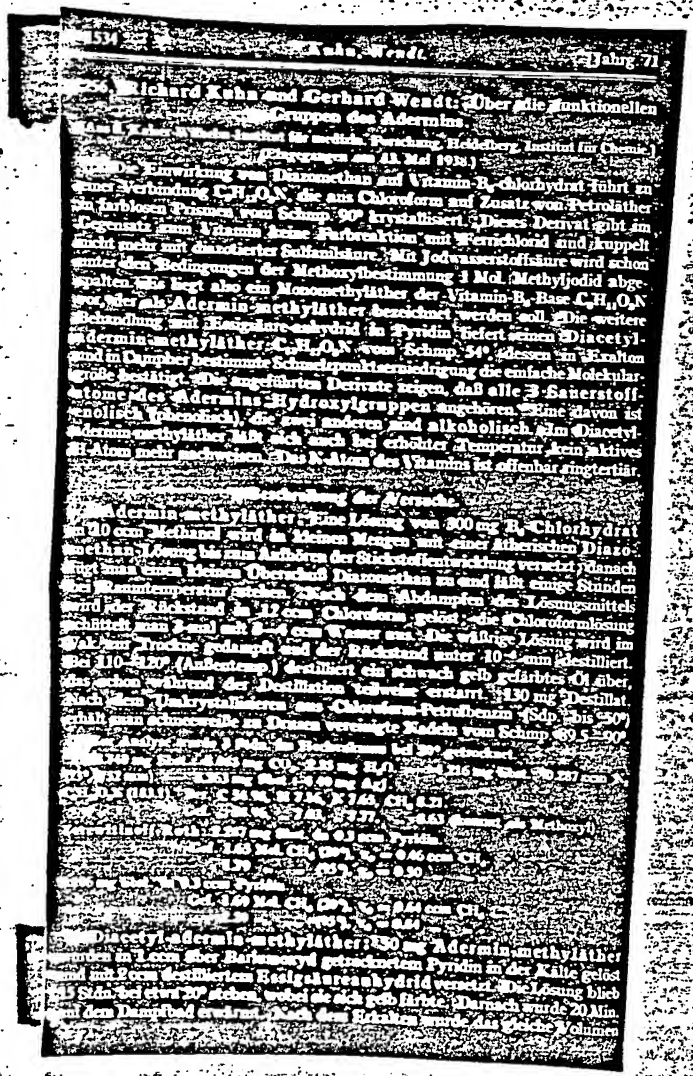
$C_{10}H_9NO_2$. Ber. C 68.57, H 5.14, N 8.00.

Gef. » 69.09, » 5.42, » 7.98.

Die wasserfreie Substanz löst sich in siedendem Aethylbenzoat und scheidet sich daraus, wenn nur sehr kurze Zeit erhitzt worden ist, in derben Nadeln wieder ab, die aber, wie ihre gelbe Farbe verräth, bereits Zersetzungsproducte enthalten. Länger andauerndes Kochen mit Aethylbenzoat zersetzt die Substanz völlig.

Tabelle 1. Einteilung der behandelten altsteinzeitlichen Kulturen.





absol. reinem Alkohol angesetzt und die Lösung im Vak. zur Trockne gedampft. Der Rückstand war ein dickflüssiges Öl, das unter 10-3 mm bei 95–100° (Luftbad) destillierte und beim Reiben sofort erstarrte. Ausb. 67 mg (92% d. Th.). Schmp. 53–54° (bkr).

[illegible] 760 mg Sbst.: 7.00 mg CO_2, 2.10 mg H_2O. — [illegible] mg Sbst.: 0.234 ccm N_2 [illegible] 748 mm). — [illegible] mg Sbst.: [illegible] ccm [illegible] NaOH [illegible] (30 Min. [illegible]).

[illegible] Ber. C 60.41, H 6.42, N 5.34, Acetyl 32.22.
Gef. [illegible] [illegible] [illegible] [illegible] 31.46.

Molekulargewichtsbestimmung nach Rast:
[illegible] 0.334 mg Sbst. in [illegible] mg Borneol ([illegible]): Δ = 7.6°. — [illegible] mg Sbst. in [illegible] mg Campher (K = [illegible]): Δ = 16.5°.
[illegible] 267. Gef. 230 (Borneol), 231 (Campher).

Zerewitinoff-Best.: [illegible] mg Sbst.: [illegible] = 0.00 ccm CH_4 (20°, [illegible])
[illegible] = 0.17 [illegible]

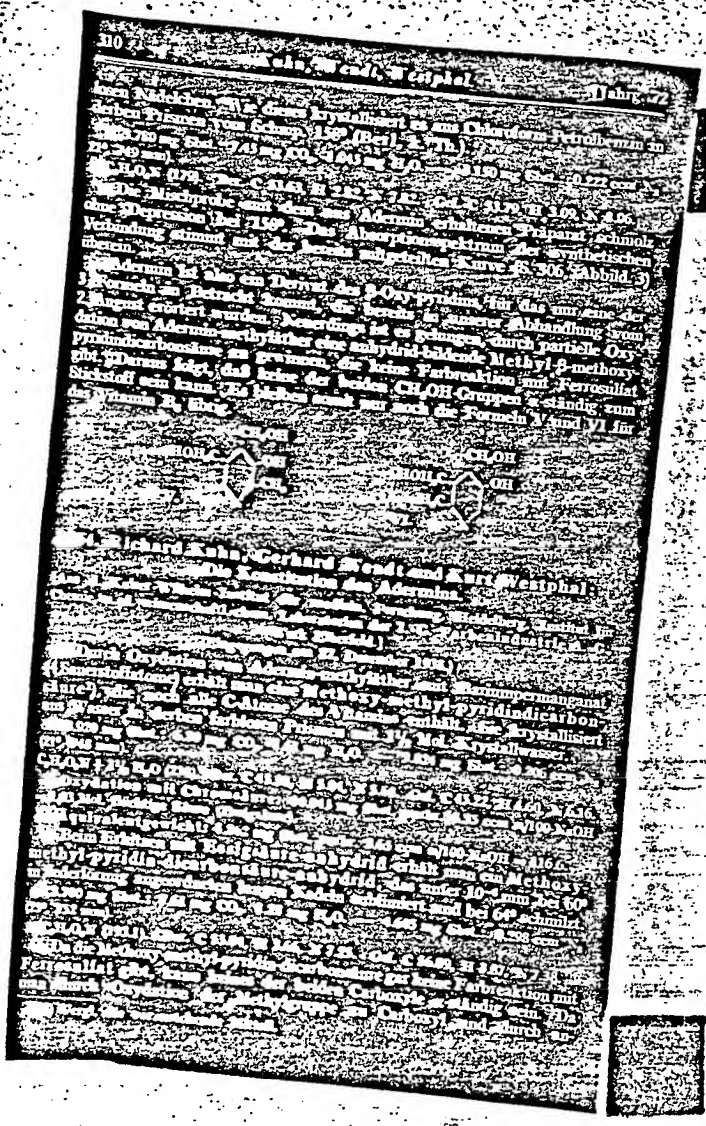
257. Richard Kuhn und Leonhard Birkofer: Zur Theorie der Mutarotation; die Mutarotation und katalytische Hydrierung der Glykosylamine sekundärer Amine.

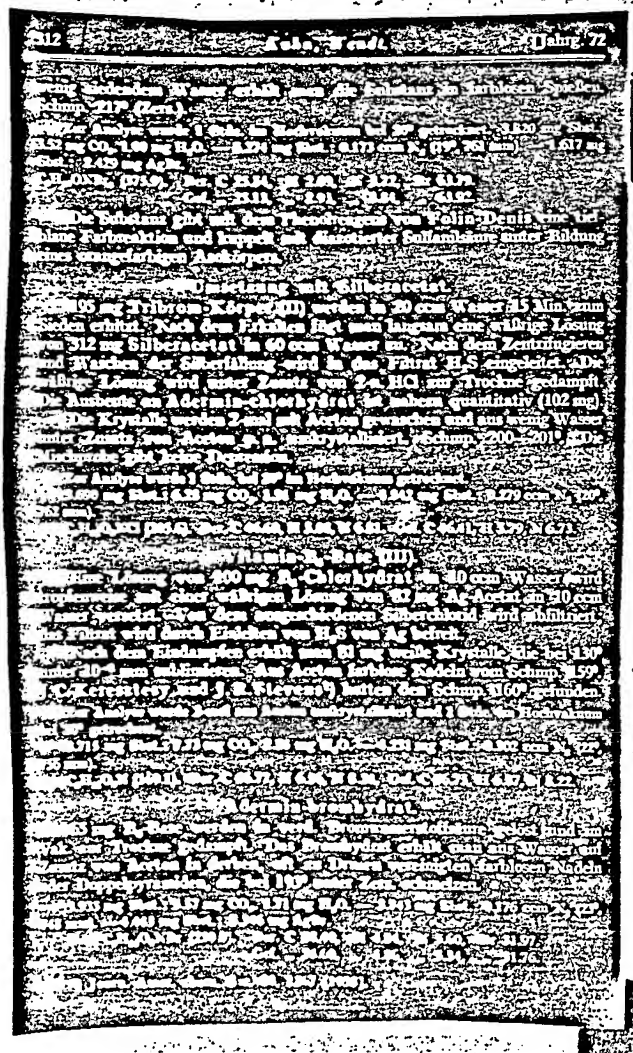
[Aus d. Kaiser-Wilhelm-Institut für medizin. Forschung, Heidelberg, Institut für Chemie.]
(Eingegangen am 22. Juni 1938.)

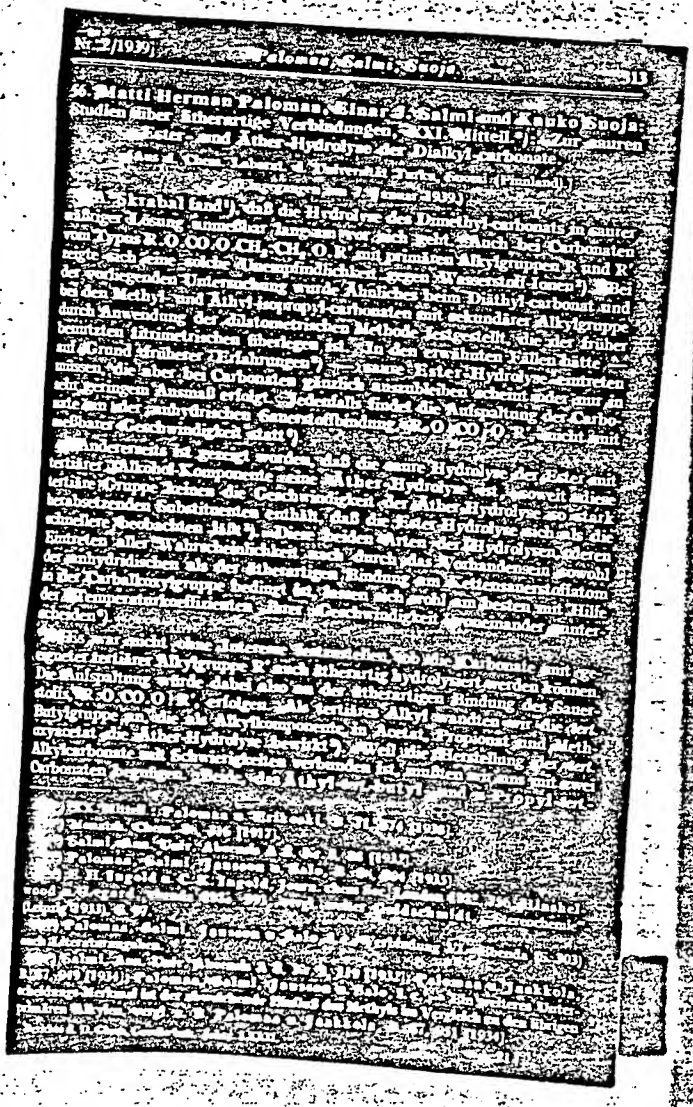
Die von Dubrunfaut[1]) 1846 entdeckte Mutarotation der Glucose ist in der Folgezeit bekanntlich bei allen reduzierenden Zuckern und vielen ihrer Derivate festgestellt worden. Die Ursache der Drehungsänderung wird seit der Auffindung der β-Glucose durch C. Tanret[2]) allgemein in der Einstellung eines echten Gleichgewichts zwischen den, nach B. Tollens[3]) ringförmig gebauten, α- und β-Formen erblickt.

Viele Forscher haben versucht, die Erscheinung durch vorübergehende Anlagerung und Wiederabspaltung von Wasser zu erklären, so C. S. Hudson[4]), T. M. Lowry[5]), E. F. Armstrong[6]), J. C. Irvine und E. St. Steele[7]) u. a. Aber all diese Vorstellungen scheinen heute hauptsächlich aus folgenden beiden Gründen verlassen zu sein. Einerseits haben J. W. Baker, Ch. K. Ingold und J. F. Thorpe[8]) in einer sorgfältigen Untersuchung über die Mutarotation der Tetramethylglucose in absolut wasserfreiem Methanol gezeigt, daß die Reaktionsgeschwindigkeit vom Zusatz steigender Wassermengen unabhängig ist, und daraus den Schluß gezogen, "that the mutarotation of sugars is essentially [illegible] phenomenon, and that neither analytical nor subanalytical traces of water intervene in the manner suggested by Lowry and Armstrong's hypotheses". Andererseits haben R. Kuhn

1) Compt. rend. Acad. Sciences 23, [illegible] (1846).
2) Bull. Soc. chim. France [3] 13, 728 (1895); [illegible] 8, 322 (1883) [illegible].
3) Journ. Amer. chem. Soc. 32, [illegible] (1910); vergl. dagegen J. Böeseken, Rec. Trav. chim. Pays-Bas [illegible] (1920); A. E. Smith, [illegible] (1922); R. Kuhn, [illegible] Chem. 118, [illegible] (1925).
4) Journ. chem. Soc. London [illegible], 1304 (1903).
5) Journ. chem. Soc. London [illegible], 1365 (1903).
6) Journ. chem. Soc. London 107, 1230 (1915).
7) Journ. chem. Soc. London 127, [illegible] (1925).







[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Synthesis of Vitamin B_6. II[1]

BY STANTON A. HARRIS AND KARL FOLKERS

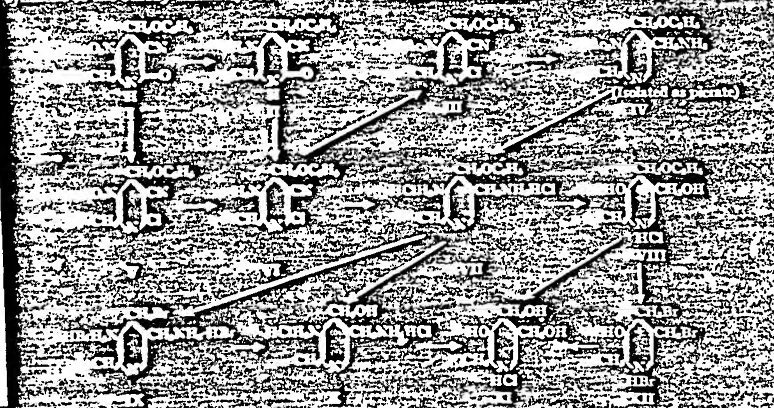
In a previous article[2] a complete synthesis of vitamin B_6 was described. The present paper describes some variations and improvements in this synthesis, along with new derivatives of some of the intermediate compounds. These variations are shown in the set of reactions, I–XII.

The original synthesis is represented by the reactions I → V → VI → VII → VIII → XII → XI. The nitropyridone, I, was prepared by the nitration of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, which in turn was prepared by the condensation of ethoxyacetylacetone and cyanacetamide.

The ethoxy-diamine, VII, is the key compound in all these syntheses. This compound was prepared by two new variations of these reactions: I → II → VI → VII and I → II → VI → III → IV → VII. These variations are limited by the low yield in reaction II → VI. Compounds III and IV are not essential to the success of the synthesis of the ethoxy-diamine, VII.

Acetylation of the aminopyridone, II, and the chloroaminopyridine, VI, gave a mono- and a diacetate in each case. The question of the position of the second acetyl group in the diacetate of the aminopyridone, II, was settled only by analogy. Since the chloro-aminopyridine, VI, also formed a diacetate and the original pyridone, namely, 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, did not form an acetate when boiled with acetic anhydride, it was deduced that the diacetate of II had both acetyl radicals attached to the amino group.

The important variations in the synthesis start with the ethoxy-diamine, VII. The first variation is represented by the reactions VII → VIII → XI. It was found that the ethoxy group of VIII could be split with dilute hydrochloric acid in a bomb tube reaction at 150°. This reaction eliminated the use of constant boiling hydrobromic acid and the necessity for the subsequent hydrolysis of the intermediate dibromide, XII. A second variation is shown by the steps VII → IX → X → XI. These steps also were shortened by another bomb tube reaction to give the third and most

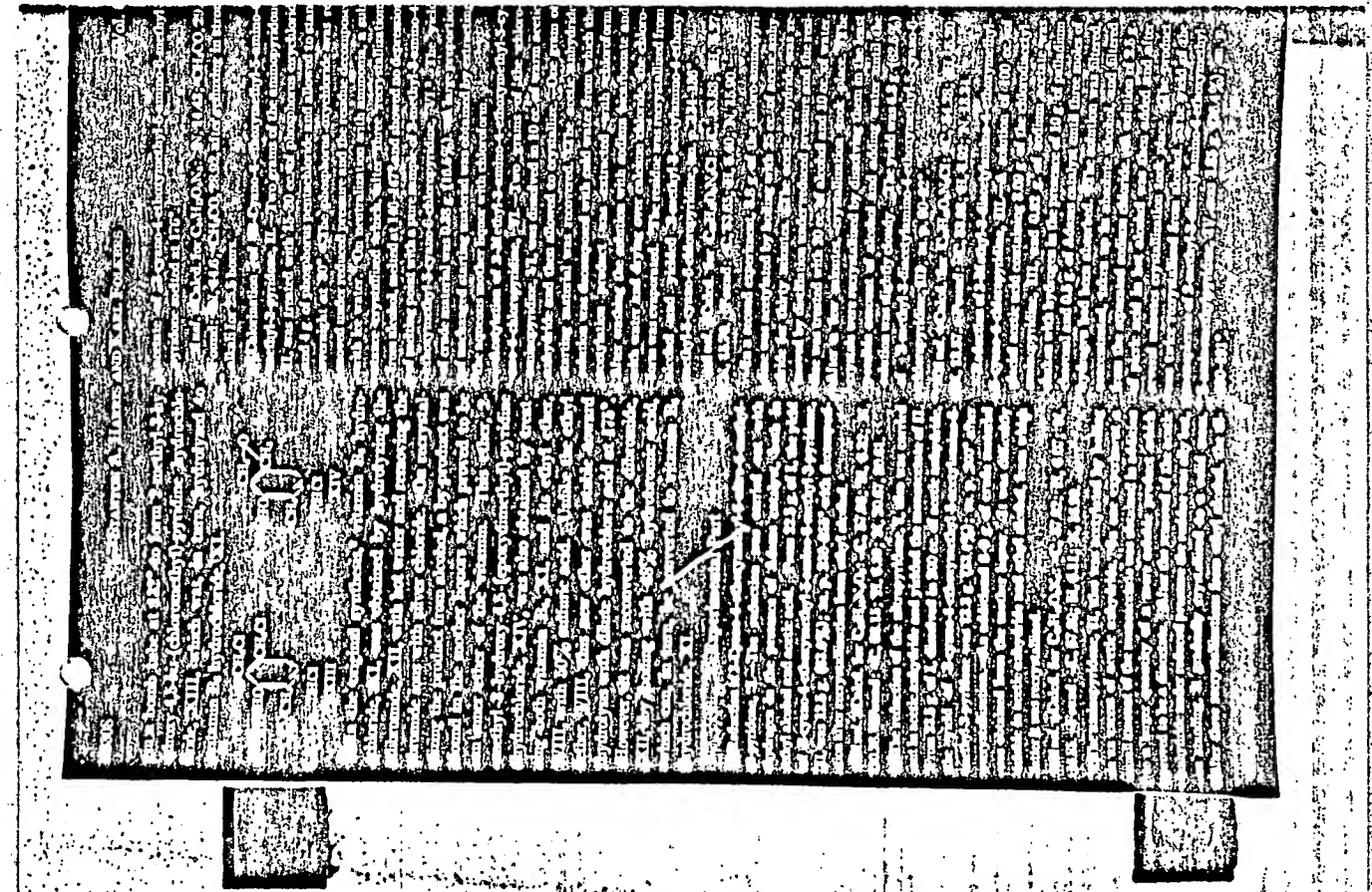


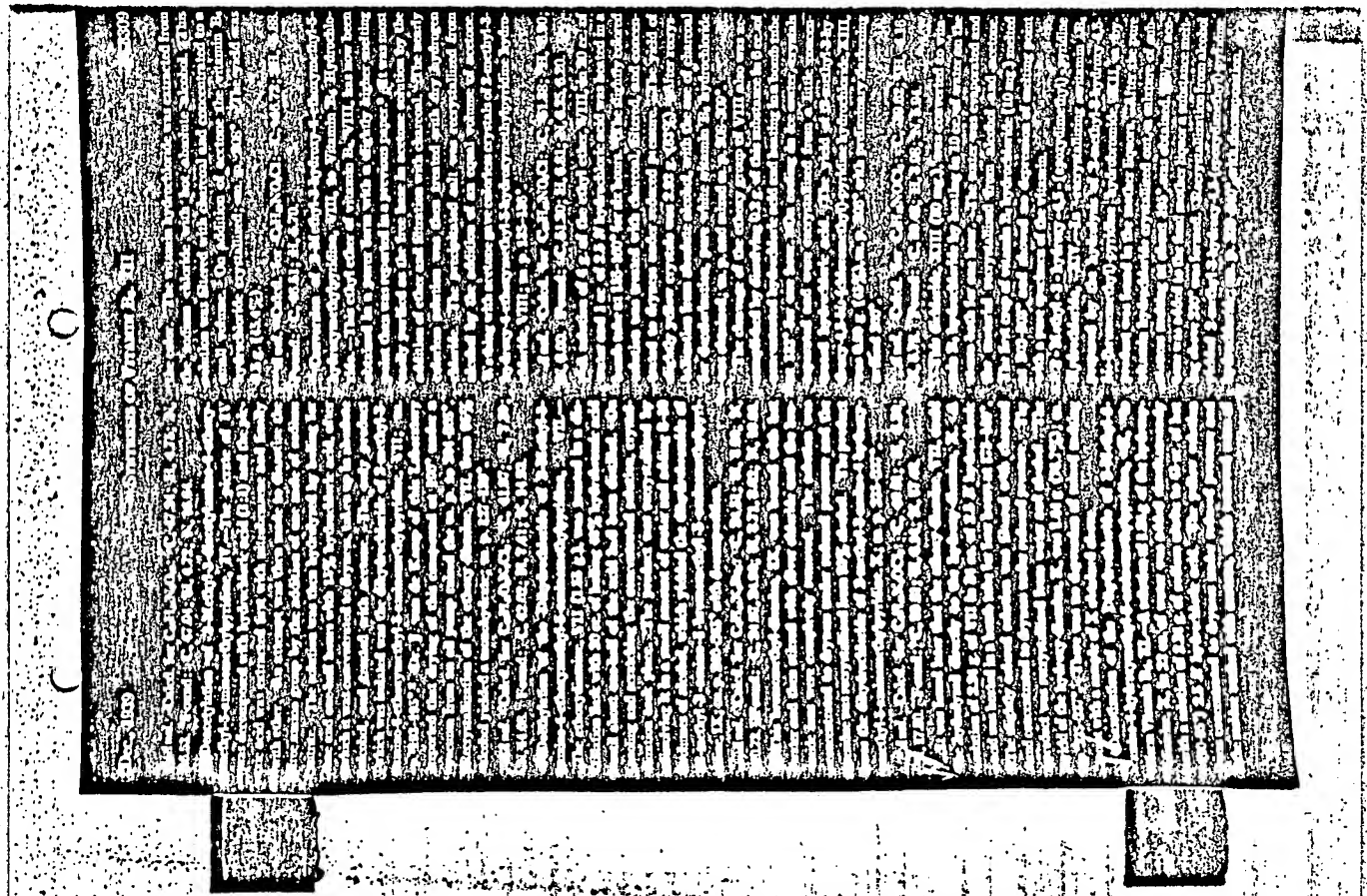
practical series of reactions, VII → X → XI. The hydroxy diamine, X, was more easily isolated and recrystallized than was the 4-ethoxymethyl derivative, VIII, of vitamin B_6.

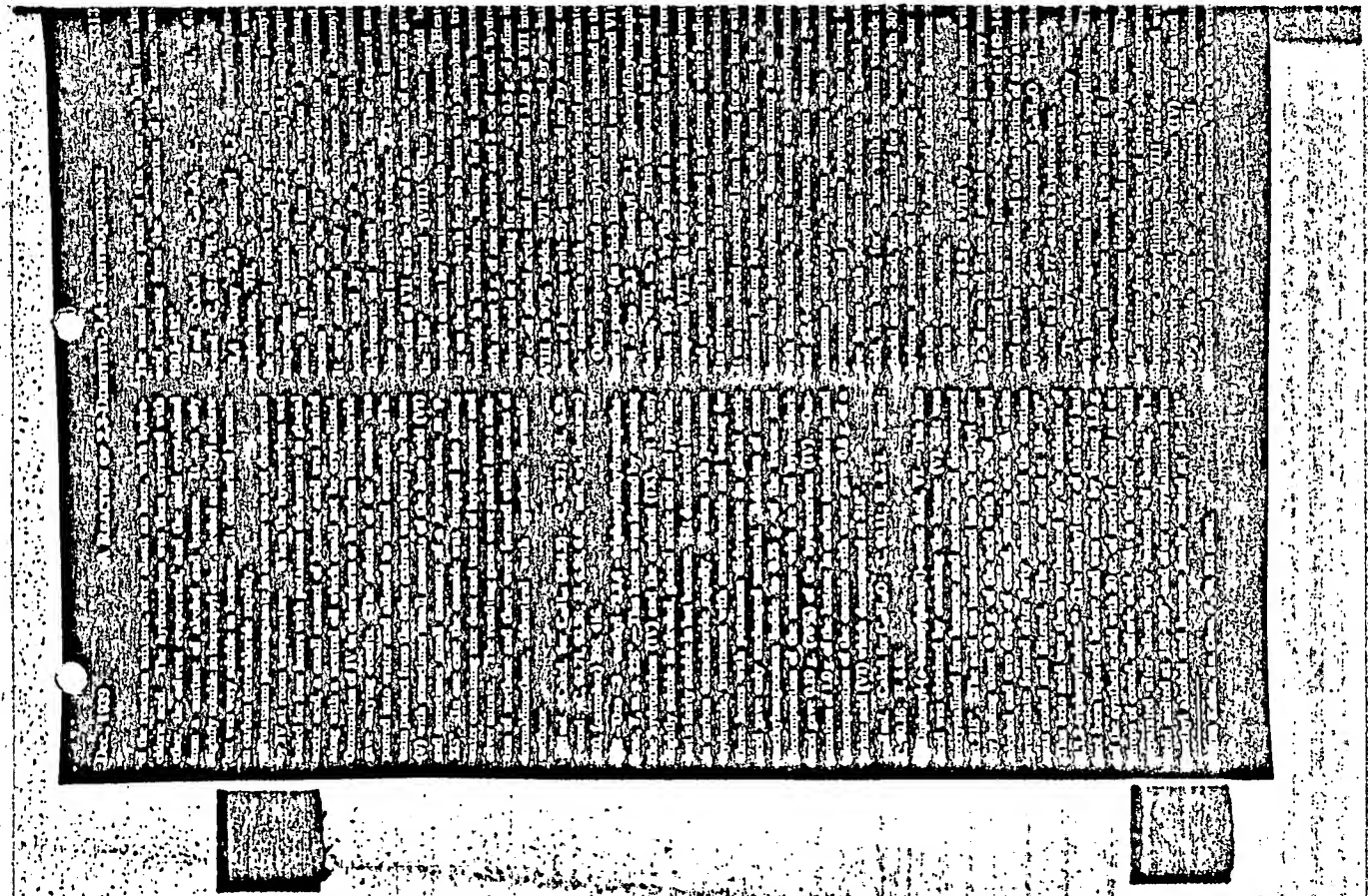
The 4-ethoxymethyl derivative, VIII, also was deethylated with concentrated hydrochloric acid

(1) [illegible] this paper was presented [illegible] Division of the American Chemical Society at Boston, [illegible] September 11, 1939.

(2) Harris and Folkers, THIS JOURNAL, [illegible]







minutes, with ammonium chloride and water, the ether extract gave 90% yields of the carbinol (IX).

Other analytical data on this compound are contained in the earlier paper[3] in which this compound was numbered (VIII).

[illegible] Oxy-2,3-dimethyl-1,1,4-triphenyldihydronaphthalene, IX, m. p. 154°.—This carbinol was formed in 90% yields by the addition of phenylmagnesium bromide to VIII. It is very unstable in the presence of acid and when an alcohol solution of the carbinol was treated with hydrochloric acid, a molecule of water was lost with the formation of the hydrocarbon (IV). IX melts at 154° with the loss of a molecule of water and the formation of the hydrocarbon (IV). Warming with zinc chloride and conc. hydrochloric acid in benzene also converted IX to the hydrocarbon (IV). The Grignard machine showed one active hydrogen. Boiling for one hour with potassium permanganate and potassium hydroxide gave 90% of unchanged material. Boiling for one hour with potassium dichromate in glacial acetic acid gave a solid from which, after many recrystallizations from alcohol and ethyl acetate, it was possible to isolate a small amount of the 235° hydrocarbon. Ozonization of IX in chloroform gave the ketone (V), so dehydration to the hydrocarbon (IV) probably occurred before the reaction with ozone.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.21, 88.95; H, 6.80, 6.75.

The 235° Hydrocarbon.—This compound, isomeric with the 180° hydrocarbon (IV), was formed in small amounts in many attempts to oxidize the hydrocarbon (IV) with potassium dichromate or potassium permanganate in glacial acetic acid or with ozone, and to oxidize the carbinol (IX) with potassium dichromate in glacial acetic acid.

Heating the hydrocarbon (IV) with acetic acid alone or with iodine in acetic acid did not convert it into the high melting isomer. Ozone converted 0.4 g. of the 235° compound into an oil from which no solid material could be obtained. The 235° compound was only slightly soluble in alcohol and in ethyl acetate, but could be crystallized from benzene.

Anal. Calcd. for $C_{30}H_{24}$ (384.2): C, 93.71; H, 6.29. Found: C, 93.84, 93.23; H, 6.29, 6.07; mol. wt. (camphor), 360.

The author wishes to thank the University of Minnesota for the courtesy shown her as an Honorary Fellow of the University while on leave from Vassar College in the spring of 1938.

Summary

Starting with the two di-addition products from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone, parallel series of reactions lead to the same product, a hydrocarbon.

Structures have been assigned to these two di-addition products, to the two compounds resulting from the dehydration and rearrangement of these compounds, and to four new compounds obtained in these series of reactions.

POUGHKEEPSIE, N. Y. RECEIVED AUGUST 24, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXVI. Oxidation and Reduction Products of Equilenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In previous work from this Laboratory it was observed that equilenin when reduced with Adams catalyst in acidic ethanol gave approximately a 70% yield of 5,7,9-estratrienol-17. No other reduction products were isolated. Ruzicka, Müller and Mörgeli[2] in a somewhat similar reduction obtained this same product in addition to some α-dihydroequilenin. By modifying the reduction technique these workers were able to obtain a 5,7,9-estratrienediol-3,17 which was identical with one of the diols obtained by the reduction of equilenin with sodium.[3,4]

When the hydrogenation of equilenin is carried out in a neutral medium with Adams catalyst, the essential product is α-dihydroequilenin, a product first isolated from the phenolic fraction of mares' pregnancy urine by Wintersteiner and co-workers[5] and later prepared by Marker and co-workers[6] by the reduction of equilenin with aluminum isopropylate. The hydrogenation of α-dihydroequilenin in acidic ethanol yields the same 5,7,9-estratrienol-17 as was obtained from equilenin, indicating that the hydroxyl group at C-17 is of the α-configuration.

In a previous comprehensive investigation of the carbinol fraction of mares' pregnancy urine,[7] we reported the isolation from the chromic anhy-

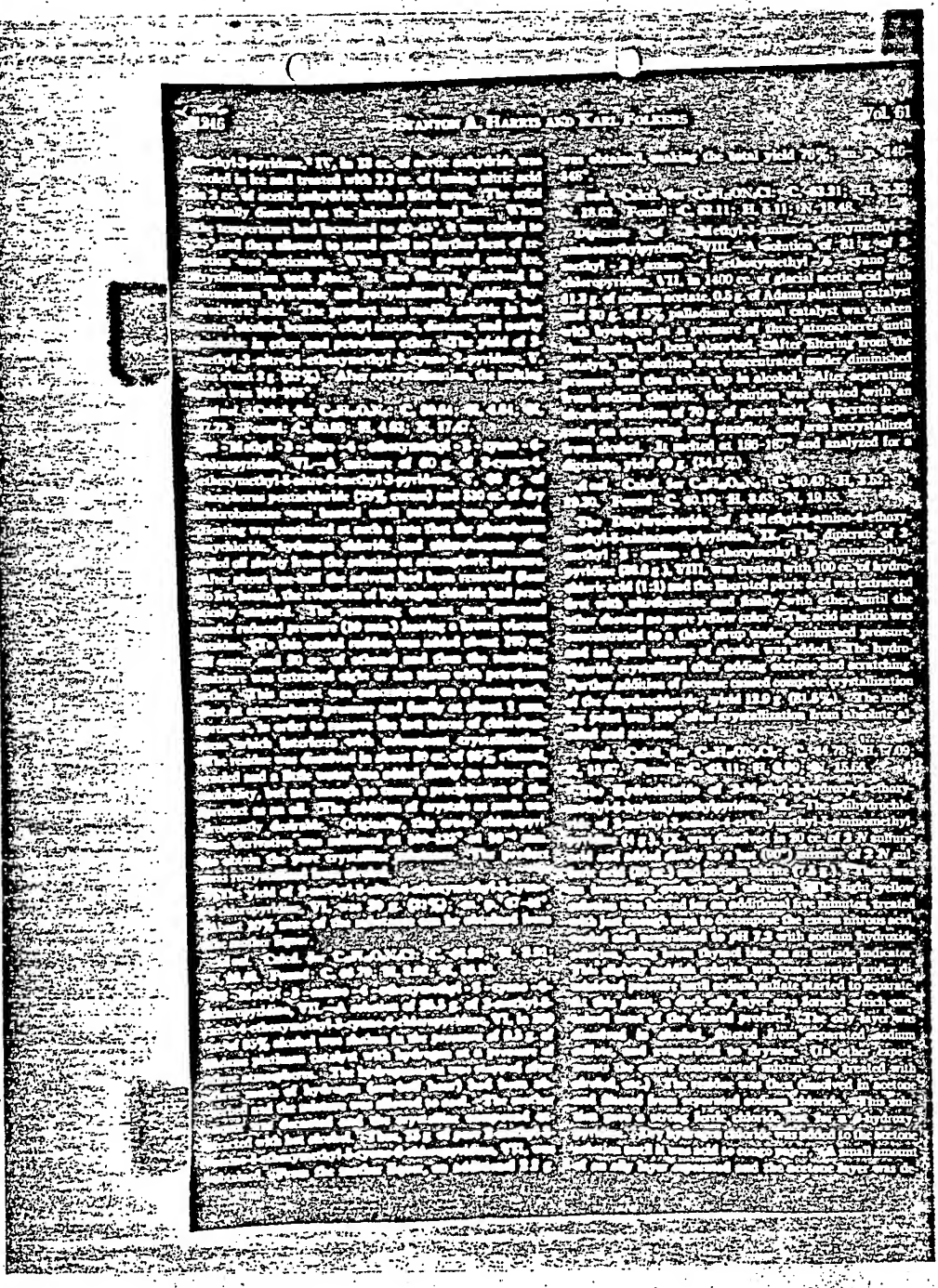
(1) [illegible] Oakwood and [illegible], This Journal, [illegible] (1937).
(2) Ruzicka, Müller and Mörgeli, Helv. Chim. Acta, [illegible] (1938).
(3) [illegible] (1938).
(4) David, [illegible] (1938).
(5) Wintersteiner, [illegible], This Journal, [illegible] (1936).
(6) Marker and Rohrmann, This Journal, 61, [illegible] (1939).

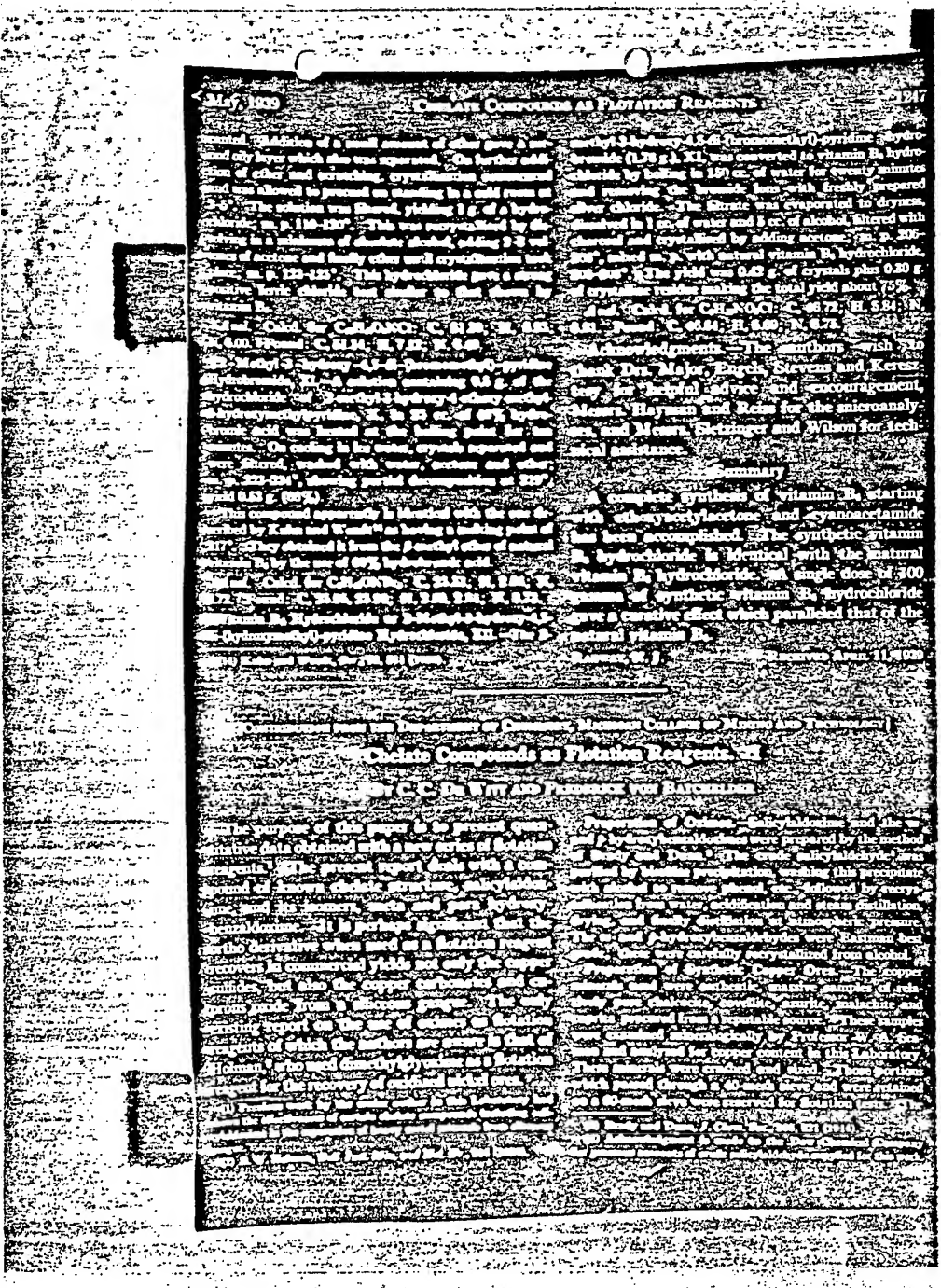
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Synthesis of Vitamin B12

BY D. M. BONNER, A. R. TODD AND A. H. COOK

RECEIVED JULY 5, 1949





[illegible] Harris, Eric T. Stiller and Karl Folkers

[illegible] for their assistance in the preparation of [illegible] used in this work.

Summary

[illegible] The methyl ether of vitamin B_6 was oxidized to give a lactone $C_{11}H_{13}NO_4$ and a diacid $C_{10}H_{11}NO_5$. The acid was shown to be 3-methyl-5-methoxypyridine-4,6-dicarboxylic acid. Vitamin B_6 was shown to be 3-methyl-5-hydroxy-4,6-di-(hydroxymethyl)-pyridine.

[illegible] March 15, 1939

[illegible] Harris and Folkers

[illegible]

[illegible] from the Merck Laboratories of Merck & Co., Inc.]

Structure of Vitamin B_6. [illegible]

By Sharrow A. Harris, Eric T. Stiller and Karl Folkers

[illegible] this paper deals with the synthesis of the [illegible] acid $C_{11}H_{13}NO_4$, I, and the lactone $C_{11}H_{11}NO_3$, II, which were obtained by Stiller, Keresztesy and Stone[1] by the oxidation of the methyl ether of vitamin B_6. The synthetic lactone and acid were found to be identical with the corresponding compounds obtained from vitamin B_6. [illegible] conclusive proof is furnished that vitamin B_6 is 3-methyl-5-hydroxy-4,6-di-(hydroxymethyl)-pyridine, III. The synthesis may be represented graphically in the following sequence:

[illegible]

The synthesis of VI is similar to the synthesis of 2-methyl-3-hydroxy-4,5-dicarbethoxypyridine, XIII, which was obtained by the condensation of acetylacetic ester and cyanoacetamide as previously described [illegible] of the Stiller and Folkers[2] condensation of IV and V might have led to 2-methyl-3-hydroxy-4-carbethoxy-5-carbamidopyridine, XIV. The proof that the product had structure VI instead of XIV was shown by its conversion on pyridolysis to VII, which was obtained in 65% yield. It is obvious that the pyridone derivative, XIV, would be incapable of giving a lactone on pyridolysis. The pyridone derivative, VI, [illegible] gave as much as 80% yield with no evidence of any other product being formed.

Experimental Part

[illegible]

of piperidine were added with shaking. Since the mixture became warm, it was necessary to cool the solution. Crystals soon appeared. The mixture was allowed to stand overnight, cooled and filtered. The product was washed with 95% alcohol. The yield of white crystals was 92 g. or 81%, m. p. 209–210°, corr. The product was purified by crystallization from boiling 95% alcohol; m. p. 210°.

Anal. Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.38; H, 6.19; N, 14.80.

The Lactone of 3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII.—Fifteen grams of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone was mixed with 125 cc. of concentrated hydrochloric acid and heated at 120–125° for four hours. The reaction mixture was then poured into 400 cc. of water and ice mixture, whereupon the lactone of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII, crystallized. It was filtered, and washed with water. The dried product weighed 11.1 g. or 87%. The product was recrystallized from water; m. p. above 320°.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.24; N, 8.48. Found: C, 58.14, 57.90; H, 4.19, 4.19; N, 8.46.

The following method was used later and was found to be preferable. A solution of 93 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, VI, in 1120 cc. of 50% sulfuric acid, was refluxed for three hours. The temperature of the liquid was 120°. The reaction mixture was then poured into 3.5–4.0 liters of water and placed in the ice room overnight. On the following day, the crystals were filtered off, washed well with water, alcohol, and ether, and dried at a moderate temperature, 55–60°. The yield of VII was 70.5 g. or 88.5%.

The Lactone of 3-Carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone, VIII.—A solution of 28 g. of the lactone of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII, in 62 cc. of concentrated sulfuric acid was added to an ice-cold mixture of 134 cc. of concentrated sulfuric acid and 32 cc. of fuming nitric acid (sp. gr. 1.5). The mixture warmed spontaneously to a temperature of 35 to 45°. After the temperature had started to fall the mixture was cooled to 15° and poured onto crushed ice. The final volume was about one liter. A yellow solid formed immediately which was filtered and dried at 65°. The yield of the lactone of 3-carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone was 29.6 g. or 83.5%. On recrystallization from water, it melted at 270–280° with decomposition.

Anal. Calcd. for $C_8H_6N_2O_5$: C, 45.71; H, 2.88; N, 13.33. Found: C, 45.82; H, 2.82; N, 13.21.

The Lactone of 2-Methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX.—About 15.2 g. of the lactone of 3-carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone, VIII, 50 cc. of phosphorus oxychloride and 75% excess of phosphorus pentachloride were mixed and refluxed until solution occurred (three-quarters of an hour). The phosphorus oxychloride was distilled off under reduced pressure, whereupon a solid separated. This was dissolved in benzene, filtered, and the product precipitated by adding petroleum ether. The total yield of the lactone of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX, was 12.6 g. or 77%. The product was recrystallized from benzene or ethyl acetate; m. p. 176–178°.

Anal. Calcd. for $C_8H_5N_2O_4Cl$: C, 42.01; H, 2.19; N, 12.25. Found: C, 41.96; H, 2.10; N, 12.44.

The Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X.—A solution of 21.3 g. of the lactone of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX, in 250 cc. of glacial acetic acid, with 0.4 g. of platinum oxide catalyst, was shaken with hydrogen at three atmospheres' pressure, until three moles had been absorbed. The solution was cooled, filtered and the crystalline precipitate well washed with ether. The net yield of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X, was 8.7 g. or 47.7%. After recrystallization from alcohol, the m. p. was 280–282°.

Anal. Calcd. for $C_8H_7N_2O_2Cl$: C, 48.36; H, 3.53; N, 14.11. Found: C, 48.32; H, 3.46; N, 14.28.

The Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XI.—A suspension of 5.95 g. of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X, and 10 g. of 5% Pd–BaCO$_3$ catalyst in 250 cc. of absolute alcohol was shaken with hydrogen at three atmospheres pressure at 60°. The absorption of hydrogen stopped after one mole had been used and, on cooling, spontaneous crystallization of a chlorine-free compound took place. After recrystallization from alcohol, the m. p. was 224–226°. The yield of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XI, was 4.3 g. or 87.5%.

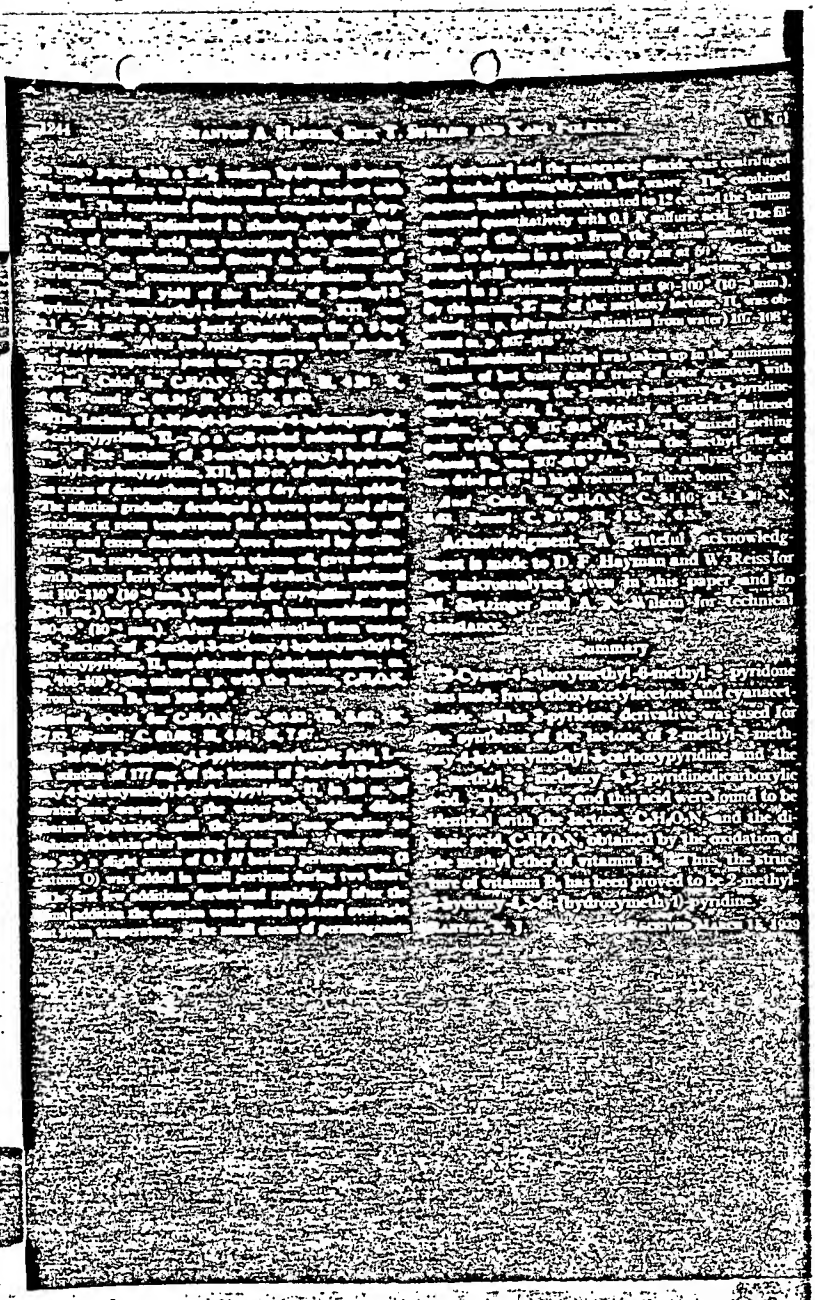
Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.54; H, 4.88; N, 17.07. Found: C, 58.62; H, 4.78; N, 17.07.

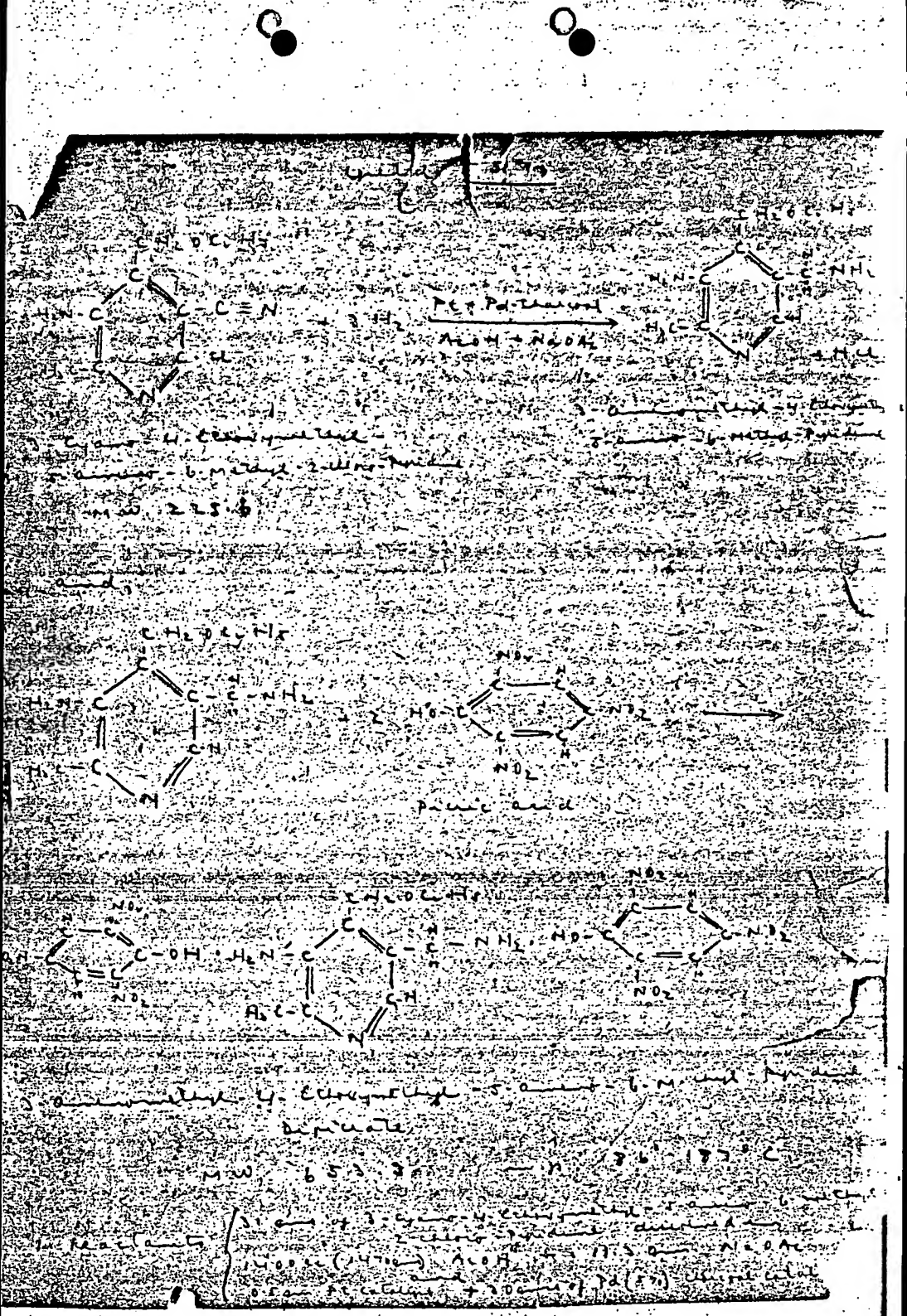
The aminopyridine derivative, XI, was also made directly from the nitrochloropyridine derivative, IX, by dissolving 20.37 g. of the lactone of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX, in a mixture of 1 liter of ethyl acetate and 1 liter of 95% alcohol, and shaking with hydrogen in the presence of 0.75 g. of platinum oxide catalyst and 20 g. of 5% Pd–BaCO$_3$ catalyst. The first three moles of hydrogen was absorbed in fifteen minutes, whereas it took several hours to absorb the fourth mole. It was filtered from the catalyst, concentrated to dryness and recrystallized from water in the presence of charcoal. The yield of XI was 12.1 g. or 82.5%; m. p. 226°.

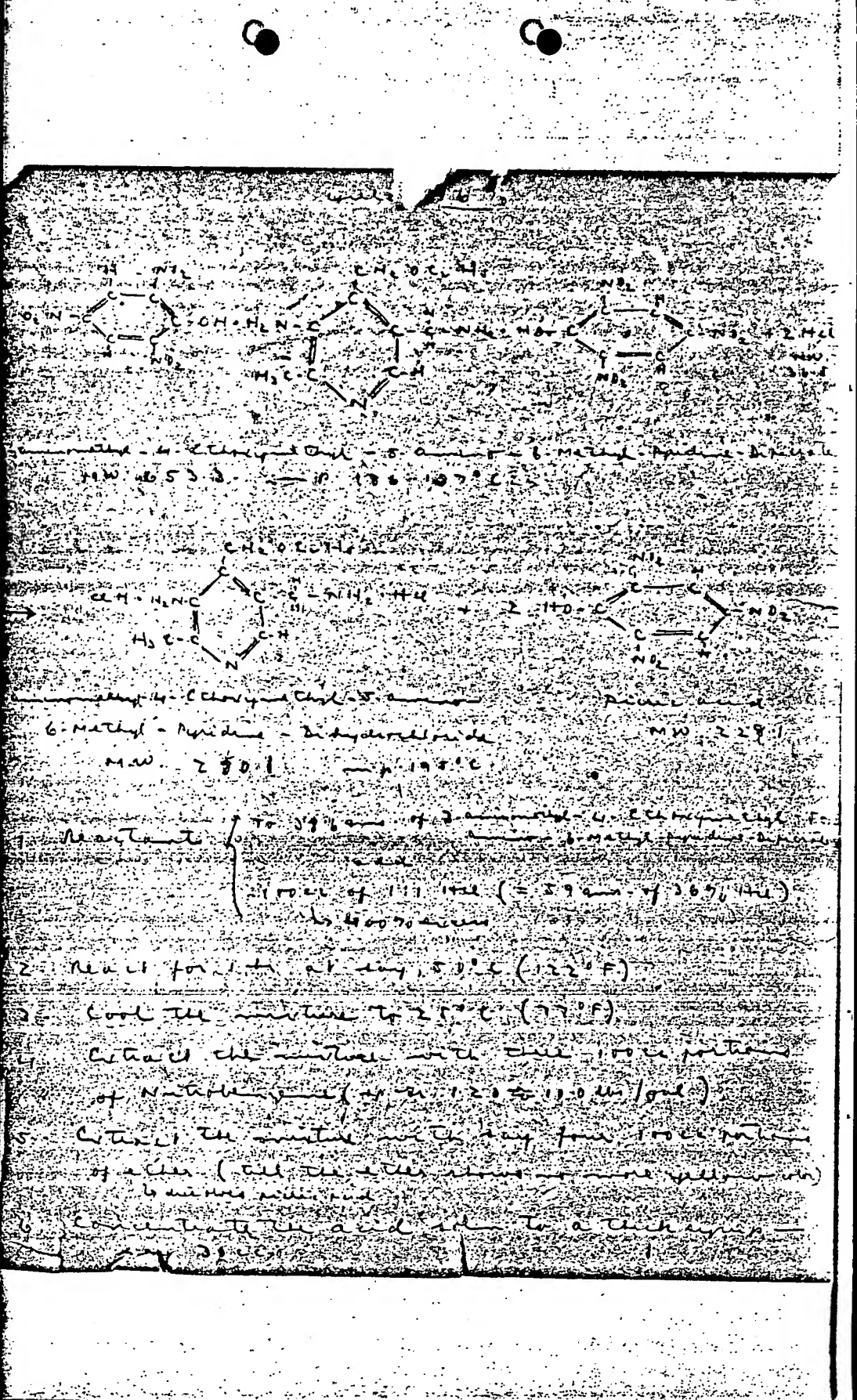
The Picrate of the Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxypyridine.—The above aminopyridine derivative, XI, may be isolated nearly quantitatively as its picrate by adding an alcoholic solution of picric acid to an alcoholic solution of the amine. It was recrystallized from alcohol; m. p. 229–230°.

Anal. Calcd. for $C_{14}H_{11}O_9N_5$: C, 42.75; H, 2.80; N, 17.81. Found: C, 42.68; H, 2.82; N, 17.73.

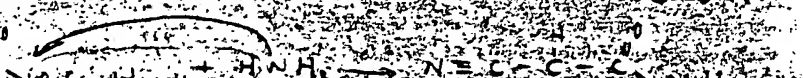
The Lactone of 2-Methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine, XII.—To 4.85 g. of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XI, dissolved in 100 cc. of 25% sulfuric acid, and cooled in ice, was added a slight excess of sodium nitrite (2.1 g. in 10 cc. of water). This diazo solution was added slowly to 25 cc. of a boiling 50% sulfuric acid solution. After the addition was complete, the solution was cooled and neutralized







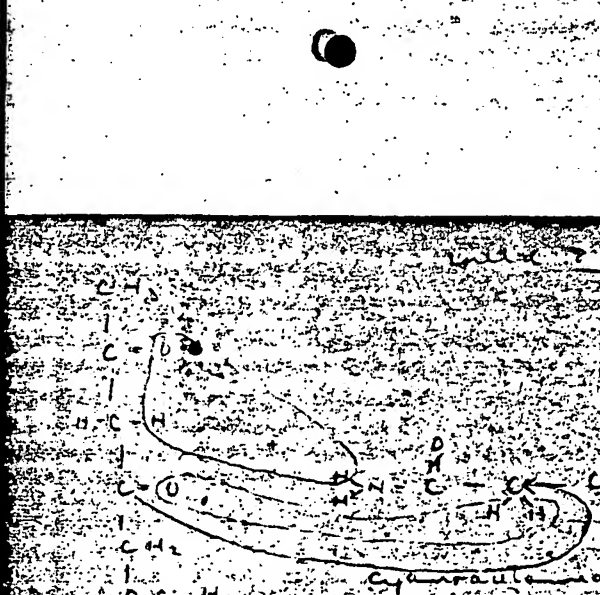
Yield: 87 %



ethyl cyanoacetate — M.W. 113.1

cyanoacetohydrazide — m.p. 128–130 °C — M.W. 99.0

1. From 4 moles of ethyl cyanoacetate, 4 moles of 64 % aqueous NH_2NH_2 and 2 volumes of absolute ethanol.
2. When the reaction is complete (TLC), cool to −8 °C (+ 18 °F).
3. Filter the product.
4. Wash the product with two 50 cc portions of −8 °C ethyl alcohol.
5. Dry in air.
6. Dissolve in 400 cc of hot (75 °C ≈ 167 °F) ethyl alcohol.
7. Cool to 10 °C (50 °F). Crystals deposit quantitatively.
8. Filter the crystals.
9. Wash with 50 cc of −8 °C ethyl alcohol.
10. Dry in air.



1. Dissolve 6.53 gms of cyanoacetamide in 5.0 cc of 95% alcohol.
2. Add 9.1 gms of ethoxymethylenecyanoacetic ester and 8.5 cc (7.1 gms) of piperidine with agitation and cooling. Crystals soon appear. Keep in refrigerator at 0°C (32°F) for 2 hrs.
3. Filter the crystals.
4. Wash the crystals twice with 2.0 cc portions of 95% EtOH.
5. Dissolve the crystals in about 75.0 cc of hot 95% EtOH.
6. Cool to 10°C to obtain a crop of purified crystals.
7. Filter the crystals.
8. Wash with 2.0 cc of 10°C alcohol.
9. Dry the crystals.

9. Slowly add 2 cc of the titrant (0.1 M solution) to precipitate the nitrosoguanidine, shielding the solution at 0°C.
10. Filter the nitrosoguanidine crystals.
11. Wash twice with three portions of water at 0°C.
12. Dissolve the crystals in 25 cc of water at 50°C.
13. Cool the solution to 30°C.
14. Add 250 cc of petroleum ether to precipitate the nitrosoguanidine crystals.
15. Filter the crystals.
16. Wash with cold water at 0°C.
17. Dry the crystals.

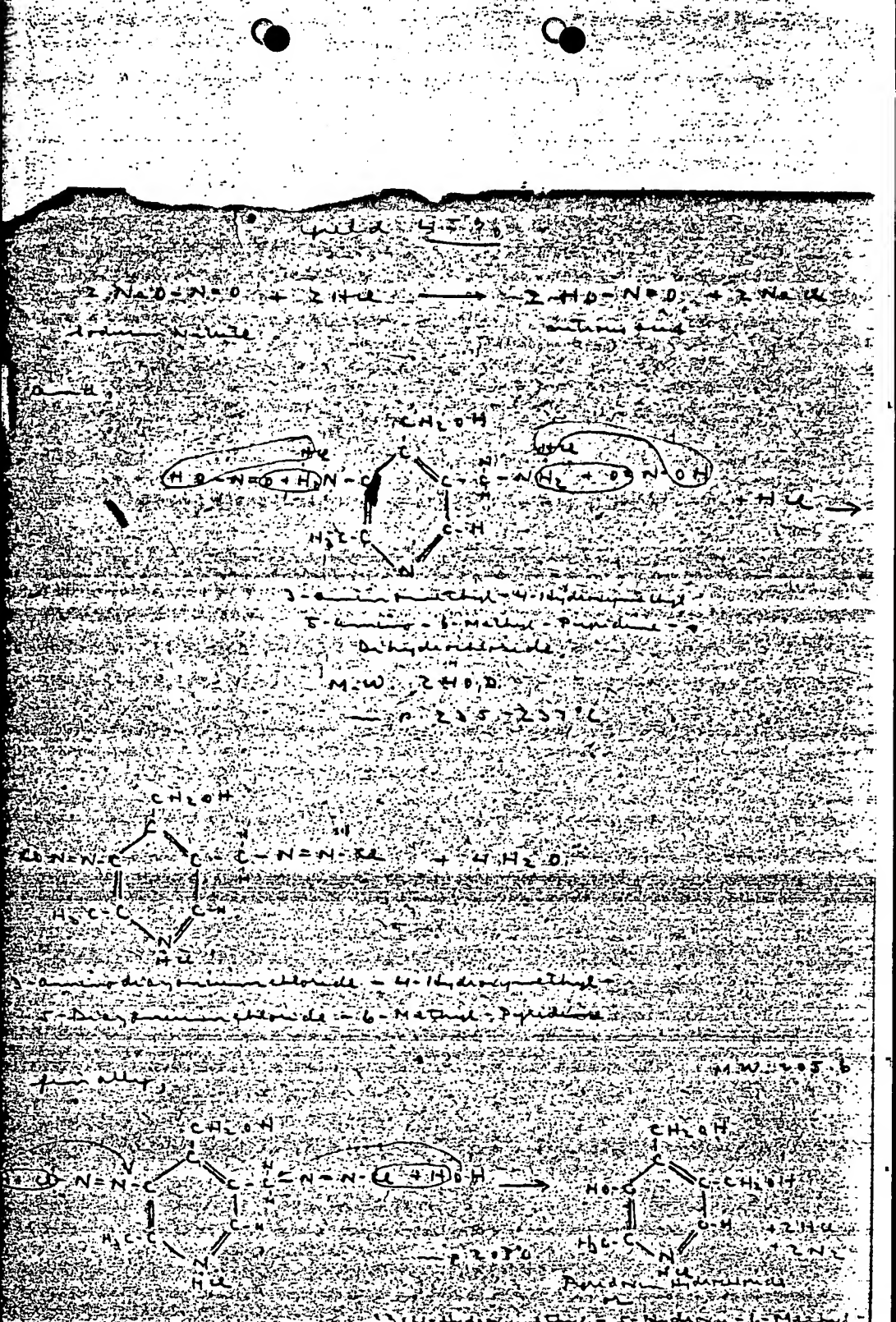
cool the residue and add 100 cc of H2O
200 cc of 95% ethanol.
Extract the resulting mixture 10 times with
10 times with 100 cc (50 cm) portions of
petroleum ether.
Concentrate the extract first at atmospheric
pressure (to remove of the solvent)
and then at a vacuum of 1 mm
This is done in order to remove the last
traces of chloroform which interfere
with subsequent crystallization
Discard the residue and 500 cc (400 cm) of 95%
ethanol
Cool the solution to any 10°C and add a
little H2O slowly. This is done to re-
duce the solubility and not to remove
any of the precipitation of the product
as an oil.
Add a few crystals of seed to obtain the
final crystalline white-almost white product
Filter the crystals
Dissolve the crystals in 500 cc of 95%
aqueous ethanol 10°C and add a little water
ethanol and add a little water
aqueous add a few seed crystals to obtain a pure
filter the pure crystallized material
Dissolve the crystals in 2 lit of ethanol

15. Evaporate the ethanol [illegible]
(20 : 1) from 10 to 6 ml
16. Cool the solution to 10°C
17. add a little H_2O
18. add a few seed crystals to induce crystallization
19. Filter the crystals
20. Recrystallize the crystals in 60% of ethanol
21. Cool to 10°C
22. add a little H_2O
23. add a few seed crystals to induce crystallization
24. Filter the crystals
25. Dissolve the crystals in 30 ml of ethanol and add the solution to the flask with 14 ml of

9. Load the evaporated water dish to the crystals from
10. Filter the crystals
11. Extract the crystals with cold distilled water of the ethanol
12. Evaporate the ethanol solution to dryness
13. Load the ethanol extract to the crystals from
14. Combine the crystal ethanol solution from 7 and 13 and filter
15. Dry the crystals in air

1. Warm Hoal a pressure of 3 atmospheres (gauge)
2. Cool (≈ 0.7 °C) and release pressure
3. Filter out the catalyst
4. Concentrate the soln to ca 100 cc under vacuum
5. add 100 cc of ethanol to precipitate the NaCl
6. Filter out the NaCl
7. add 200 cc of ethanol containing 10 cm of pure acid
8. add a few drops of the dipivalate amine reagent and to yield a crystal
9. Filter the crystals
10. Dissolve the crystals in 500 cc of hot ethanol
11. Evaporate the soln to ca 100 cc
12. cool the soln to 10 °C to obtain a crop of crystals
13. Filter the crystals
14. Dry the crystals in air

7. Add 150 cc of acetone and a few drops of conc. HCl to the dihydrochloride - Chloroquine Diphosphate and stand for 3 hrs. till a lot of crystals form
8. Filter off the crystals
9. Wash twice with 25 cc portions of acetone
10. Dissolve the crystals in 150 cc of a mixture of 75 cc acetone + 75 cc absolute ethanol
11. Evaporate the solution to dryness
12. Cool to 10°C
13. Add 150 cc of acetone at 10°C and keep the said crystals of Dihydrochloride - Chloroquine Diphosphate for 3 hrs till crystallization is complete
14. Filter the crystals
15. Dry the crystals in air



1. Dissolve [illegible] of 3-hydroxy-4-methoxybenzaldehyde in 5 cc of 5-methyl furan-2-carboxaldehyde + 2 cc of H2O.

2. Add the hydroxylamine soln to the [illegible] dissolved in 45 cc of NH4OH (= 9.1 cc of 29% NH4) at 95°C (20°F).

3. Concentrate the soln to dryness under vacuum.

4. (NOTE - The soln is yellow colored.)

5. Wash the residue with one 5 cc portion of acetone to remove some of the yellow color.

(NOTE - The vitamin D6 HCl is only slightly soluble in acetone).

6. Extract the Vitamin D6 HCl with four 100 cc portions of hot absolute ethanol.

7. To the alcohol soln of the Vitamin D6 HCl add 0.075 gm of activated carbon.

8. Filter the soln.

9. Concentrate the alcohol soln to only 2 cc.

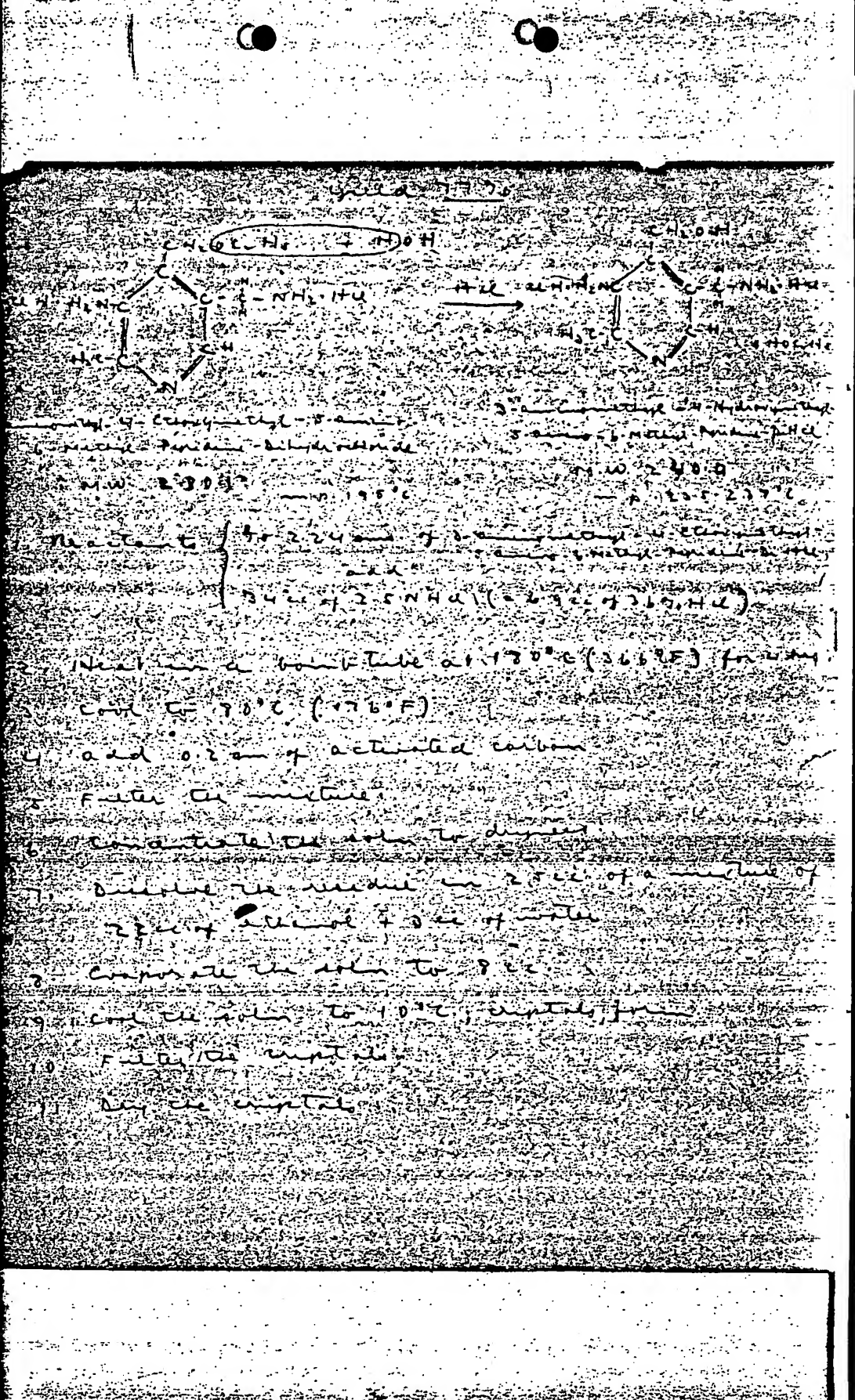
10. Cool the soln to 5°C.

11. Add 10 cc of acetone to precipitate the Vitamin D6 HCl.

12. Filter the crystals.

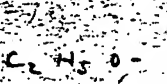
13. Wash the crystals with 2 cc of acetone at 5°C.

14. Dry the Vitamin D6 HCl crystals



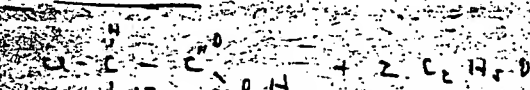
Exp 1

Monochloro acetic acid

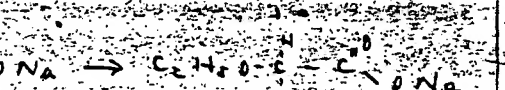


Ethyl-Ethoxy-acetate

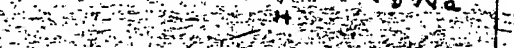
1. Reaction

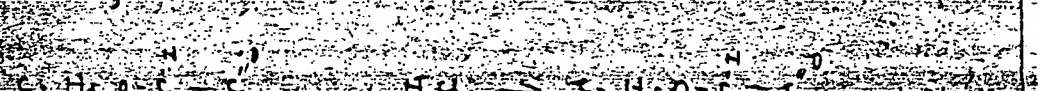


Monochloro acetic acid

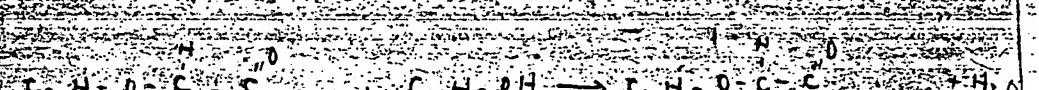


Na salt of Ethoxy acetic acid





Ethoxy-acetic-acid



Ethyl-Ethoxy-acetate

2. Reactants

Monochloro acetic acid

Absolute alcohol

Sodium Metal

Step (cont'd)

3. Reagents

Hydrochloric acid (3 to 1)

Hydrochloric acid 1 in 5

Sodium carbonate

4. Yield

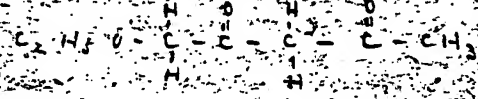
5 B 70

5. Unit operations

$A_{10} - D_2 - E_5 - D_8 - E_3 - G_1 - H_2 - V_{16} - L_1 - N_1 - P_{20}$

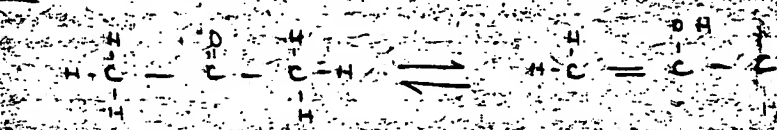
6. Solvents

Ethyl ether



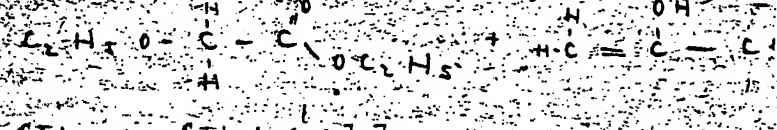
Ethoxy - acetyl - acetone

1. Reaction

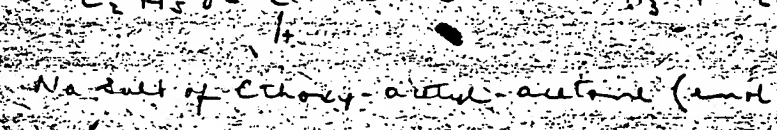


- acetone -

and,

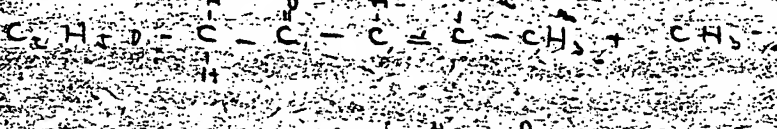


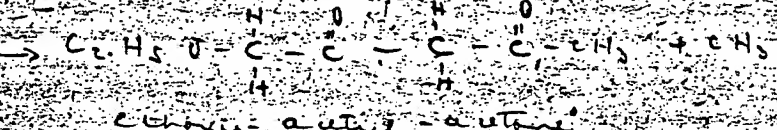
Ethoxy - ethyl acetate



Na salt of ethoxy - acetyl - acetone (enol form)

Or,





ethoxy - acetyl - acetone

Step 2

2. Reactants

Ethyl-Cinnamyl acetate

acetone

Iodine

3. Reagents

acetic acid

Copper Sulfate

Sulfuric acid

4. Yield

32%

5. Unit operations

$A_{19} - B_3 - C_3 - D_2 - H_1 - J_{12} - L_3 - N_3 - P_{30}$

6. Solvents

Benzene

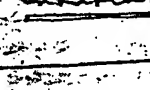
Ethyl Ether

Ethyl alcohol (absolute)

Exp. 1

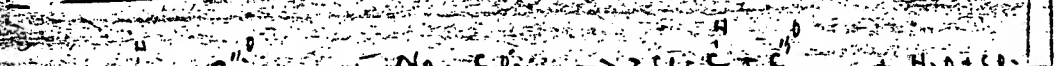
Aim

monochloro-acetic acid



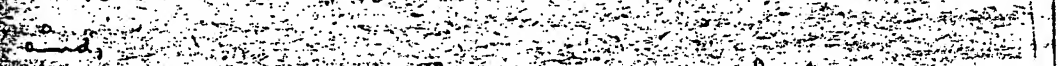
Cyano-ethyl acetate

Reaction



monochloro-acetic acid,

and,

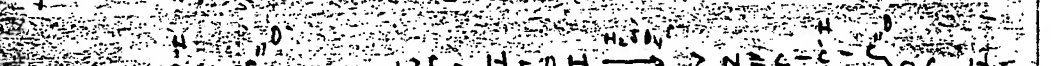


Na salt of Cyano-acetic acid

then

Cyano-acetic acid

finally,



absolute alcohol

Cyano-ethyl acetate

Exp. C-1 (cont'd) D2

2. Reactants

monosodium - acetic acid

Sodium cyanide

Ethyl alcohol (anhydrous)

3. Reagents

Sodium carbonate

Hydrochloric acid

Sulphuric acid

4. Yield

7.7 g

5. Characterization

$A_{18} - B_3 - C_8 - D_3 - E_1 - H_3 - J_{12} - L_2 - P_{16}$

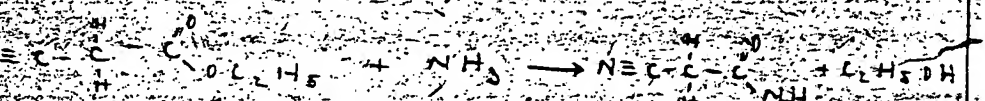
6. Solvents

Ethyl alcohol (95% H_2O)

Benzene

Cyanoacetamide

1. Reaction



Cyano ethyl acetate — Cyanoacetamide

2. Reactants

Cyano - ethyl acetate

ammonia (aqueous)

3. Reagents

None

4. Yield

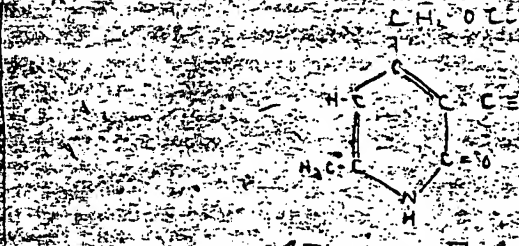
87 %

5. Unit Operations

A - D - C4 - I2 - J2 - L2 - N2 - P1

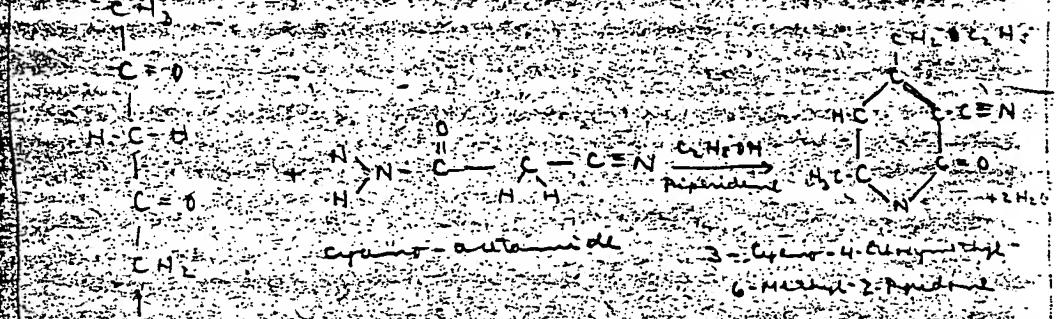
6. Solvents

Ethyl alcohol



3-Cyano-4-Ethoxymethyl-6-Methyl-2-Pyridone

1- Reaction



Ethoxy-acetyl-acetone

Cyano-acetamide

3-Cyano-4-Ethoxymethyl-6-Methyl-2-Pyridone

2- reactants

Ethoxy-acetyl-acetone

Cyano-acetamide

3- Reagents

Name

4- yield

5- Time of reaction

6- Solvents

Ethyl alcohol (95%)

Piperidine

7- Mechanism

$A_2 - B_1 - C_4 - I_1 - J_3 - L_2 - N_1 - P_3$